





INVITED REVIEW

Impact of solute carrier transporter gene polymorphisms on serum creatinine concentrations in healthy volunteers

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Abstract

In this study, we investigated the impact of single nucleotide polymorphisms in solute carrier (SLC) transporters, that is, *SLC22A7* c.1586+206A>G, *SLC22A2* c.808G>T, *SLC22A3* c.1233G>A, *SLC47A1* c.922-158G>A, and *SLC47A2* c.-130G>A, on serum creatinine (SCr) concentrations. This cross-sectional study included residents who participated as volunteers in a health promotion study. Lifestyle data, blood chemical analysis data, and SLC gene polymorphism information were collected from each participant. Univariate analyses were carried out to determine differences between groups and correlations in SCr. Stepwise multiple regression analysis was performed to confirm the independence of factors that were significantly different in the univariate analyses. In multiple regression analyses, muscle mass, serum cystatin C concentrations, body fat percentage, serum albumin concentrations, and *SLC47A2* c.-130G/G had the highest contribution to SCr concentrations, in that order (standardized regression coefficients = .505, .332, -.234, .123, and .084, respectively). The final model explained 72.2% of the variability in SCr concentrations. The *SLC47A2* c.-130G>A polymorphism may affect creatinine dynamics in the proximal tubules. Further studies are needed to determine the effects of SLC transporter gene polymorphisms on SCr concentrations in patients with various diseases in real-world clinical settings.

KEYWORDS

muscle mass, serum creatinine, solute carrier transporter, tubular secretion, *SLC47A2* polymorphism

1 | INTRODUCTION

Determination of the glomerular filtration rate (GFR) is crucial in the overall assessment of kidney function.^{1,2} Estimated GFR (eGFR) is

used to diagnose chronic kidney disease and individualize the renal-excretion drug dosage, for example.³ GFR should be assessed using substrates that are completely filtered by the glomerulus without tubular secretion or reabsorption. Intravenously administered

Abbreviations: Cr, creatinine; Cys-C, cystatin C; eGFR, estimated GFR; GFR, glomerular filtration rate; SCr, serum creatinine; SLC, solute carrier.

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inulin does not bind to proteins *in vivo*, is completely filtered by the glomeruli, and shows neither tubular secretion nor reabsorption.^{4,5} Therefore, inulin is strongly recommended as the gold standard for GFR measurement.^{4,5} However, the invasive administration of inulin, an exogenous substance, is a cumbersome method, requiring timed urine collections over several hours, and is costly.

Creatinine (Cr) and cystatin C (Cys-C) are well-known endogenous substances used for assessing GFR.³ Cr is a 113-Da metabolite of muscle catabolism and has long been proposed as a glomerular filtration marker.² Because measuring Cr is easy and inexpensive, calculation of eGFR based on Cr is widely available and appropriate for use as a first-line tool.⁶ GFR can be estimated based on serum Cr (SCr) concentrations, age, sex, and body size.³ Cr does not bind to proteins *in vivo* and is freely filtered across the glomerulus, but is also secreted in the proximal tubules. Therefore, Cr clearance is 20%–30% higher than inulin clearance because inulin is filtered only in the glomeruli.⁷ In addition, Cr metabolite is primarily proportional to muscle mass, although many other factors, such as nutritional status and thyroid function, also affect Cr metabolism.^{8,9} Therefore, eGFR monitoring based on SCr concentrations is affected by intra-individual variability in Cr metabolite and tubular secretion.¹⁰ Furthermore, Cys-C is a 13-kDa cysteine proteinase inhibitor protein that is produced by all nucleated cells at a steady rate and is freely filtered by the kidney, with near-complete reabsorption and catabolism in the proximal tubule and no significant urinary excretion.¹¹ However, the usefulness of serum Cys-C (SCys-C) monitoring in assessing eGFR in real-world clinical practice needs further assessment with regard to both variability in measurement values between laboratories and cost-effectiveness.¹¹

Cr is secreted into the urine via drug transporters, such as organic anion transporter 2 (OAT2, encoded by *SLC22A7*), organic cation transporter 2 (OCT2, encoded by *SLC22A2*), OCT3 (encoded by *SLC22A3*), multidrug and toxin extrusion protein 1 (MATE1, encoded by *SLC47A1*), and MATE2-K (encoded by *SLC47A2*) in the proximal tubules.¹² Therefore, differences in the activities of these SLC transporters can cause individual variations in the kinetics of Cr in the proximal tubules. In the clinical setting, inhibitors of these SLC transporters are commonly used, and elevated SCr concentrations have been reported in patients taking these drugs.¹³ If the contribution of Cr tubular secretion to SCr concentrations in individual patients could be predicted, assessment of the glomerular filtration capacity based on eGFR, which is calculated using SCr concentrations, would be more accurate.

Single nucleotide polymorphism (SNP) variations in these SLC transporters have been also known to influence the pharmacokinetics and/or pharmacodynamics of these substrate drugs.^{14,15} Twin studies have shown that eGFR calculated using SCr or SCys-C concentrations has a strong heritable component.¹⁶ Recently reported genome-wide association studies (GWASs) have identified SNPs that may affect eGFR calculated using SCr concentrations, based on data from over a million individuals.^{17,18} In the results of these GWASs, several SNPs have been identified that may affect Cr metabolism and tubular secretion. However, not all of the previously reported SNPs with functional effects for drug transporters expressed in the

proximal tubules were also identified in these GWASs. In addition, eGFR reflects the effects of metabolism and glomerular filtration of Cr, as well as various diseases and medications taken. Therefore, in order to examine the influence of drug transporter gene polymorphisms expressed in the proximal tubules that affect the tubular secretion of Cr, it is necessary to conduct epidemiological studies that exclude, as much as possible, the various biases that may be latent in real-world data.

The purpose of this study was to investigate differences in SCr concentrations between genotypes at the SNP sites of *SLC22A7* c.1586+206A>G (>5.9% allele frequency), *SLC22A2* c.808G>T (>10.9% allele frequency), *SLC22A3* c.1233G>A (>48.6% allele frequency), *SLC47A1* c.922-158G>A (>40.3% allele frequency), and *SLC47A2* c.-130G>A (>33.6% allele frequency), which have been reported to have functional effects in previous studies^{14,15,19} and are commonly found in the Japanese population (>5% in the National Center for Biotechnology Information database, <http://www.ncbi.nlm.nih.gov/SNP>).

2 | MATERIALS AND METHODS

2.1 | Study design and participants

The Iwaki Health Promotion Project is a large-scale epidemiological survey conducted annually in the Iwaki district of Hirosaki city, Japan.²⁰ Our study is a secondary analysis of data from this project. This survey targeted residents older than 20 years of age living in this area. This cross-sectional study included residents who participated in this survey in 2016. This study was approved by the Ethics Committee of Hirosaki University Graduate School of Medicine (authorization number: 2016-028), and all participants provided written informed consent prior to participation in the study. All participants enrolled in the study voluntarily in response to a public announcement.

In 2016, 1148 individuals were enrolled in this study. Of these participants, those who met the following exclusion criteria were excluded from the study (Figure 1). Participants were excluded if they did not have SCys-C concentration data ($n = 3$) and did not have SLC transporter gene polymorphism information ($n = 29$). In addition, participants with diabetes ($n = 58$); immunoglobulin A nephropathy ($n = 2$); body mass index (BMI) greater than or equal to 25 ($n = 281$); SCr concentrations more than the normal upper limit in our laboratory (male, >1.04 mg/dL; female, >0.79 mg/dL; $n = 59$); free triiodothyronine (FT3), free thyroxine (FT4), or thyroid stimulating hormone (TSH) concentrations outside the normal range for our laboratory (2.30–4.00 pg/mL, 0.90–1.70 ng/dL, or 0.50–5.00 μ IU/mL, respectively; $n = 112$); and concurrent medications ($n = 652$) were excluded from this study.

2.2 | Data collection

Age, sex, and medication history data were collected using a self-report questionnaire. Body fat percentage and muscle mass were

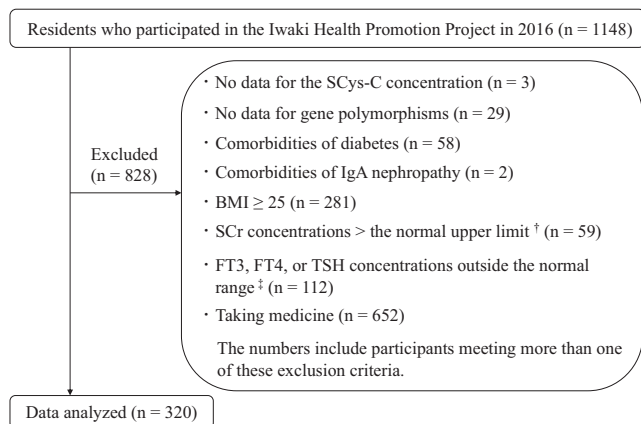


FIGURE 1 Flow diagram for participant selection. BMI, body mass index; FT3, free triiodothyronine; FT4, free thyroxine; IgA, immunoglobulin A; SCr, serum creatinine; SCys-C, serum cystatin C; TSH, thyroid stimulating hormone. [†]Male, >1.04 mg/dL; female, >0.79 mg/dL. [‡]2.30–4.00 pg/mL, 0.90–1.70 ng/dL, and 0.50–5.00 μ IU/mL, respectively.

measured using the bioelectrical impedance method with a Tanita body composition analyzer MC-190 (Tanita Corporation). Participant height and weight were measured on the day of the health check, and BMI and body surface area (BSA) were calculated using the following equations:

$$\text{BMI (kg/m}^2\text{)} = \text{weight / height}^2$$

$$\text{BSA (m}^2\text{)} = \text{weight}^{0.425} \times \text{height}^{0.725} \times 0.007184$$

Blood samples were collected from the peripheral vein in the sitting position early in the morning after fasting. The samples were immediately centrifuged to separate the serum, placed in tubes containing EDTA, and stored at -80°C until analysis. Serum concentrations of albumin, Cr, Cys-C, blood urea nitrogen, uric acid, aspartate aminotransferase, alanine aminotransferase, FT3, FT4, and TSH were determined (LSI Medience Corp.). SCr and SCys-C concentrations as markers of renal function were measured using the enzymatic method and latex agglutination turbidimetry method, respectively.

2.3 | Genotyping

SNP genotypes of the participants were determined using the Japonica array, an SNP array designed specifically for the Japanese population.²¹ The array contains 659 253 SNPs, including tag SNPs for imputation and phenotype-related SNPs from previously reported genome-wide analyses and pharmacogenomics studies. *SLC22A7* c.1586+206A>G (rs4149178), *SLC22A2* c.808G>T (rs316019), *SLC22A3* c.1233G>A (rs2292334), *SLC47A1* c.922-158G>A (rs2289669), and *SLC47A2* c.-130G>A (rs12943590) genotypes were determined using these data.

TABLE 1 Demographic and clinical characteristics of the participants (n = 320)

	Number (%)	
Male	148 (46.3)	
Female	172 (53.8)	
	Mean \pm SD	(Min–Max)
Age (year)	46.6 \pm 13.5	(20–87)
Body weight (kg)	57.0 \pm 9.5	(37.2–79.7)
BSA (m ²)	1.61 \pm 0.17	(1.20–2.00)
Body fat percentage (%)	22.4 \pm 6.8	(5.9–40.8)
BMI (kg/m ²)	21.3 \pm 2.2	(14.5–24.9)
Muscle mass (kg)	42.0 \pm 8.4	(28.0–62.0)
Biochemical data		
Serum albumin (g/dL)	4.55 \pm 0.29	(3.2–5.4)
Serum creatinine (mg/dL)	0.71 \pm 0.13	(0.39–1.04)
Serum cystatin C (mg/L)	0.70 \pm 0.10	(0.43–0.99)
Blood urea nitrogen (mg/dL)	13.4 \pm 3.3	(6.2–24.3)
Uric acid (mg/dL)	5.1 \pm 1.3	(1.6–8.5)
AST (IU/L)	21.3 \pm 6.6	(11–54)
ALT (IU/L)	19.1 \pm 10.5	(5–79)
FT3 (pg/mL)	3.35 \pm 0.35	(2.4–4.0)
FT4 (ng/dL)	1.26 \pm 0.16	(0.9–1.7)
TSH (μ IU/mL)	1.61 \pm 0.85	(0.51–4.52)

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BSA, body surface area; FT3, free triiodothyronine; FT4, free thyroxine; Max, maximum; Min, minimum; SD, standard deviation; TSH, thyroid stimulating hormone.

2.4 | Statistical analysis

The distributions of continuous variables were evaluated using the Shapiro–Wilk test and histograms. Continuous data from demographic and clinical information were presented as means \pm standard deviations, minima and maxima, or medians (interquartile ranges). Allele frequencies of gene polymorphisms were evaluated according to the Hardy–Weinberg equilibrium using chi-square tests. One-way analysis of variance or Student's *t* tests and correlation tests with Pearson's correlation coefficient (*r*) values were used to determine differences and correlations between groups with continuous values for normal distributions. Kruskal–Wallis tests or Mann–Whitney *U* tests and correlation tests with Spearman's ρ values were used to determine differences and correlation between groups with continuous values for non-normal distributions. In comparisons among the three groups, if the *p* values were <.05, the difference between the two groups was analyzed by Student's *t* tests or Mann–Whitney *U* tests with Bonferroni correction. Stepwise multiple regression analysis was performed to confirm the independence of factors that were significantly different in the univariate analysis. However, to avoid multicollinearity, for factors that were clearly physiologically related, the factor with the largest *r* value in the univariate analysis was entered in the multivariate analysis. Each SLC transporter

gene polymorphism was categorized as “wild-type homozygotes and other genotypes” or “mutant-type homozygotes and other genotypes.” That is, they were replaced by dummy variables and entered into the stepwise selection multiple linear regression analysis. The percent variation that could be explained by the stepwise selection multiple regression equation was expressed as a coefficient of determination (R^2). Results with p values of $<.05$ were considered statistically significant. Statistical analyses were performed with SPSS 27.0 for Windows (SPSS IBM Japan Inc.).

3 | RESULTS

In total, 320 individuals were included in the study. The demographic and clinical data of the participants are shown in Table 1. The average age was 46.6 ± 13.5 years, and 53.8% of the participants were women. Because this study included a large number of healthy participants, there was little variation in the biochemical data.

The genotype and allele distributions of each SLC transporter gene polymorphism are shown in Table 2. The distributions of *SLC22A7* c.1586+206A>G, *SLC22A2* c.808G>T, *SLC22A3* c.-1233G>A, *SLC47A1* c.922-158G>A, and *SLC47A2* c.-130G>A genotypes were in agreement with the Hardy-Weinberg equilibrium ($p = .246, .795, .716, .937, \text{ and } .775$, respectively).

The relationships of SCr concentrations with demographic features, clinical characteristics, and SLC transporter genotypes are shown in Table 3. The best correlation with the SCr concentration was muscle mass ($r = .731, p < .001$). In addition to muscle mass, there were relationships between SCr concentrations and body fat percentage, uric acid concentrations, BSA, body weight, and SCys-C concentrations with correlation coefficients $>.5$ ($r = -.624, .591, .583, .537, \text{ and } .503$, respectively). Moreover, as shown in Figure S1, clear statistical relationships were found between muscle mass and sex, body weight, and BSA. In addition, body fat percentage was also related to sex and BMI. However, weak statistical relationships were found between muscle mass and body fat percentage. In addition, there were significant differences in SCr concentrations

among *SLC47A2* c.-130G>A genotypes for five SLC transporter polymorphisms ($p = .017$). The p values followed by Bonferroni correction for comparisons between each genotype were 0.014 (G/G vs. G/A), 0.620 (G/G vs. A/A), and 1.000 (G/A vs. A/A).

Furthermore, when all factors were entered as explanatory variables in the multivariate analysis, sign reversal concerning slopes in the results of the univariate analysis was observed in body weight, BMI, and FT3. Therefore, sex, body weight, BSA, BMI, and FT3 were excluded from the explanatory variables entered in this multivariate analysis to avoid multicollinearity. Independent factors that influenced SCr concentrations are shown in Table 4. Five independent factors were identified by stepwise multiple linear regression analysis. The *SLC47A2* c.-130G>A genotype was an independent factor influencing SCr concentration ($p = .005$). Muscle mass, SCys-C concentration, body fat percentage, serum albumin concentration, and *SLC47A2* c.-130G>A had the highest contribution to SCr concentrations, in that order (standardized regression coefficients = $.505, .332, -.234, .123, \text{ and } .084$, respectively). The final model explained 72.2% of the variability in SCr concentrations.

4 | DISCUSSION

In this study, we found that the *SLC47A2* c.-130G>A polymorphism affected SCr concentrations. Although inhibitors of SLC transporters are known to increase SCr concentrations,²² the impact of the *SLC47A2* c.-130G>A polymorphism has not been reported in previous GWASs.^{17,18} Approximately 20% of Cr is secreted from the proximal tubules in individuals with normal renal function, and tubular secretion increases up to approximately 50% with a reduction in GFR.²³ Although the magnitude of the influence of the *SLC47A2* c.-130G>A polymorphism on SCr concentrations in this study was small, depending on the level of GFR, this impact may increase.

In multivariate analysis to identify factors influencing SCr concentrations, the independent effects of the *SLC47A2* c.-130G>A polymorphism were confirmed. Although the NCBI-SNP database (<http://www.ncbi.nlm.nih.gov/SNP>) currently lists over 1000 SNPs

TABLE 2 Genotypic and allelic distributions of *SLC22A7*, *SLC22A2*, *SLC22A3*, *SLC47A1*, and *SLC47A2* polymorphisms

Genotyping	Genotype			Allele	
<i>SLC22A7</i> c.1586+206A>G (rs4149178)	A/A	A/G	G/G	A	G
	281 (87.8)	39 (12.2)	0 (0.0)	601 (93.9)	39 (6.1)
<i>SLC22A2</i> c.808G>T (rs316019)	G/G	G/T	T/T	G	T
	249 (77.8)	66 (20.6)	5 (1.6)	564 (88.1)	76 (11.9)
<i>SLC22A3</i> c.1233G>A (rs2292334)	G/G	G/A	A/A	G	A
	93 (29.1)	156 (48.8)	71 (22.2)	342 (53.4)	298 (46.6)
<i>SLC47A1</i> c.922-158G>A (rs2289669)	G/G	G/A	A/A	G	A
	97 (30.3)	159 (49.7)	64 (20.0)	353 (55.2)	287 (44.8)
<i>SLC47A2</i> c.-130G>A (rs12943590)	G/G	G/A	A/A	G	A
	136 (42.5)	147 (45.9)	37 (11.6)	419 (65.5)	221 (34.5)

Note: Data are expressed as the number of participants (%).

TABLE 3 Relationships of serum creatinine concentrations with demographic features, clinical characteristics, and SLC transporter genotypes

	<i>r</i>	<i>p</i> value
Age (year)	-0.100	.075
Body weight (kg)	0.537	<.001
BSA (m ²)	0.583	<.001
Body fat percentage (%)	-0.624	<.001
BMI (kg/m ²)	0.239	<.001
Muscle mass (kg)	0.731	<.001
Serum albumin (g/dL)	0.216	<.001
Serum cystatin C (mg/L)	0.503	<.001
Blood urea nitrogen (mg/dL)	0.186	.001
Uric acid (mg/dL)	0.591	<.001
AST (IU/L)	0.229	<.001
ALT (IU/L)	0.279	<.001
FT3 (pg/mL)	0.392	<.001
FT4 (ng/dL)	0.252	<.001
TSH (μIU/mL)	-0.013 ^a	.819
	Mean ± SD (mg/dl)	<i>p</i> value
Sex		
Male	0.82 ± 0.09	<.001
Female	0.61 ± 0.08	
SLC22A7 c.1586+206A>G		
A/A	0.71 ± 0.13	.660
A/G	0.72 ± 0.13	
SLC22A2 c.808G>T		
G/G	0.70 (0.60–0.82) ^b	.685
G/T	0.70 (0.57–0.79) ^b	
T/T	0.71 (0.66–0.77) ^b	
SLC22A3 c.1233G>A		
G/G	0.70 ± 0.12	.764
G/A	0.71 ± 0.14	
A/A	0.70 ± 0.12	
SLC47A1 c.922-158G>A		
G/G	0.70 ± 0.13	.924
G/A	0.71 ± 0.14	
A/A	0.71 ± 0.13	
SLC47A2 c.-130G>A		
G/G	0.73 ± 0.13	.017
G/A	0.69 ± 0.13	
A/A	0.70 ± 0.13	

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase; BMI, body mass index; BSA, body surface area; FT3, free triiodothyronine; FT4, free thyroxine; SD, standard deviation; TSH, thyroid stimulating hormone.

^a ρ .

^bMedian (quartile range).

in SLC47A2 genes, the most well-known gene variant involved in the pharmacokinetics–pharmacodynamics of drugs, the substrate of MATE2-K, is the SLC47A2 c.-130G>A polymorphism, which is in the 5'-untranslated region.²⁴ The SLC47A2 c.-130G>A polymorphism has been reported to affect the blood concentration of metformin, a substrate of MATE2-K.²⁵ In a physiology-based pharmacokinetic model incorporating inhibition by trimethoprim in the tubular secretion of Cr via SLC transporters, MATE2-K was found to be a major transporter in the proximal tubules.¹³ In our previous study, we found that SCr concentrations were increased in more than 90% of patients taking trimethoprim, probably in relation to SLC transporter inhibition by this drug.²⁶ In this study, the group with SLC47A2 c.-130G/G had higher SCr concentrations than that with the A allele. This result is consistent with the effects of the SLC47A2 c.-130G>A gene polymorphism on the secretion clearance of metformin, a substrate of MATE2-K, in the tubules.²⁷ Additionally, myeloid zinc finger 1 is known to repress MATE2-K transcription, and this transcription factor has a higher binding affinity for the SLC47A2 c.-130G allele than for the A allele.²⁸ Therefore, the SLC47A2 c.-130G>A polymorphism may be an independent factor influencing SCr concentrations.

Muscle mass was the most important factor for predicting SCr concentrations. Cr is a metabolite generated via muscle metabolism in vivo and is excreted in urine via the glomerulus and proximal tubule.² In other words, the interpretation of this value is important for avoiding overestimation of GFR based on the SCr concentration because a decrease in muscle mass decreases the SCr concentration.² Muscle mass is lower in women, the elderly, smaller individuals, and those with poorer nutritional status. Therefore, the GFR prediction equation incorporates not only the SCr concentration but also information on sex, age, and body size, such as weight and BSA.³ That is, it is not surprising that muscle mass was found to be an independent predictor in this analysis. SCys-C concentration was also the second most influential factor after muscle mass for predicting SCr concentrations in multivariate analysis. SCys-C concentration-based eGFR more accurately reflects actual GFR than SCr concentration-based eGFR.^{29,30} Therefore, the high contribution of SCys-C concentrations in predicting SCr concentrations must reflect the influence of the glomerular filtration of Cr. The fact that muscle mass had a higher contribution to SCr concentration than did SCys-C concentration in our results may be explained by the inclusion of healthy adults as study participants in this study. That is, the reason may be that SCys-C was distributed within a narrow range of normal values. Body fat percentage was also the third most influential factor after SCys-C concentrations for predicting SCr concentrations in multivariate analysis. Xiaojie et al. reported that urinary excretion via glomerular filtration of Cr is higher in adults with higher body fat percentages.³¹ Because the body fat percentage and SCr were negatively correlated in this study, our results may support the association between high percentages for these factors and excess glomerular filtration of Cr in previous studies. Furthermore, the results of this study indicated that albumin and SCr concentrations are positively correlated. Indeed, renal function has been reported to be

TABLE 4 Stepwise multiple linear regression analysis for identifying independent variables influencing serum creatinine

Independent variable	Slope	SE	SRC	p value
Muscle mass (kg)	0.008	0.001	0.505	<.001
Serum cystatin C (mg/L)	0.418	0.040	0.332	<.001
Body fat percentage (%)	-0.005	0.001	-0.234	<.001
Serum albumin (g/dL)	0.056	0.014	0.123	<.001
SLC47A2 c.-130G/G	0.022	0.008	0.084	.005

Note: Intercept = -0.079 (SE = 0.079), $R^2 = .722$.

Abbreviations: SE, standard error; SRC, standardized regression coefficient.

overestimated in patients with hypoalbuminemia owing to increased tubular secretion of Cr.⁸ These easily interpretable results may be attributed to the fact that the participants in our study were healthy adults.

This study had several limitations. First, the sample size in our study was very small. Recently reported GWASs have identified multiple SNPs that may affect tubular secretion of Cr, based on data from over a million individuals.^{17,18} Not surprisingly, it was not possible to examine the effects of all these SNPs on SCr concentrations in our study. Therefore, future studies with larger sample sizes should examine the effects of these SNPs on SCr concentrations. Second, because of regional bias, these results may not be generalizable to other populations. Not surprisingly, the impact of ethnic differences on SCr concentrations also could not be examined in this study. Third, information on the diet and exercise history the day before the physical examination and the most recent smoking history was not obtained. These factors have been reported to affect SCr concentrations.^{32,33} However, our study was able to incorporate muscle mass, which affects Cr metabolism, and SCys-C concentrations, which reflect the glomerular filtration capacity of Cr, into this analysis as measured values. Furthermore, bias by disease and medications taken that may affect SCys-C concentrations and tubular secretion of Cr was largely excluded from this analysis. Therefore, the SLC47A2 c.-130G>A polymorphism may affect the tubular secretion of Cr. Although the results of this study suggested that the impact of the SLC47A2 c.-130G>A polymorphism on the SCr concentration in healthy adults is quite small, the contribution of tubular secretion to the renal clearance of Cr is not constant in all patients.^{23,34,35} In other words, the SLC47A2 c.-130G>A SNP information may explain the gap between SCr concentration-based eGFR and actual GFR in patients in whom the tubular secretion compensates for the reduced contribution of glomerular filtration. In addition, if transporters other than MATE2-K in the proximal tubules have reduced function, this transporter may compensate for the reduced function and mediate Cr efflux into the urine.³⁶

In conclusion, the SLC47A2 c.-130G>A polymorphism may affect Cr dynamics in the proximal tubules. Further studies are needed to determine the effects of SLC transporter gene polymorphisms on SCr concentrations in patients with various diseases in real-world clinical settings.

AUTHOR CONTRIBUTIONS

Takenori Niioka was involved in conceptualization. Satoshi Yokoyama and Takenori Niioka were involved in data analysis. Satoshi Yokoyama, Junichi Nakagawa, Masakiyo Kudo, Naoya Aiuchi, Tatsuya Seito, and Takenori Niioka were involved in data collection. Satoshi Yokoyama was involved in writing—original draft preparation. Junichi Nakagawa and Takenori Niioka were involved in writing—review and editing. Mizuri Isida, Tatsuya Mikami, Kazushige Ihara, Shigeyuki Nakaji, and Takenori Niioka were involved in project administration. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

Data are available from the Hirosaki University COI Program Institutional Data Access/Ethics Committee for researchers who meet the criteria for access to the data. Researchers need to have prior approval from the research ethics review boards of their respective affiliations.

ETHICS STATEMENT

The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of Hirosaki University Graduate School of Medicine.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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