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LETTER TO THE EDITOR Open Access

First verification of human small intestinal uric acid secretion and effect of ABCG2 polymorphisms

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Main text

The small intestine is the main digestive, absorptive, and endocrine organ; however, it has also recently emerged as an essential excretory organ. Hyperuricemia, which causes gout, is primarily induced by decreased urate excretion. The current understanding of urate excretion is based on the premise that approximately two-thirds of total urate is eliminated via the kidneys into the urine, whereas the remaining one-third is excreted through the intestinal tract. This concept originates from tracer experiments using radioisotopes conducted on a small number of individuals more than half a century ago [1]. Recent reports have suggested that the intestinal excretion pathway via the urate transporter adenosine triphosphate binding cassette subfamily G member 2 (ABCG2) plays a key role in the regulation of serum urate (SUA) levels as a complementary system of renal urate excretion [2–4]. Urate secretion from the intestine may make an essential contribution to SUA homeostasis; however, measurement of urate secretion using feces to demonstrate intestinal urate secretion is problematic because uric acid is catabolized by the gut microbiota [4]. The classification of hyperuricemia is solely based on the amount of urinary excretion in clinical practice, and the physiological role of intestinal urate secretion is underestimated. No studies have demonstrated urate secretion from the small intestine in addition to regulation of its secretion by ABCG2 in humans. To our knowledge, this is the first proof-of-concept study to directly measure urate secretion from the human intestine.

The study participants had Crohn's disease ($n=30$), simple ulcers ($n=2$), and obscure gastrointestinal bleeding ($n=2$) (Table 1). All participants were classified into three ABCG2 functional categories [100% ($n=11$), 75% ($n=18$), and 50% functional ($n=5$)] based on the genotype combinations of p.Q126* and p.Q141K previously reported [3, 4]. Our repeated measurements detected uric acid levels in the intestinal fluid of all subjects at baseline and 5 min later (Fig. 1). At baseline, the uric acid concentration in the intestinal fluid was 99.5 [Interquartile range (IQR): 10.1–194.0] pg/μL. After 5 min, the uric acid concentrations increased; the change in uric acid concentration after 5 min (ΔC_{UA}) was +119.9 pg/μL/5 min (IQR: 44.7–476.4, $p<0.001$), demonstrating that urate is secreted into the intestinal lumen.

ABCG2 dysfunctional single nucleotide polymorphisms (SNPs) tended to decrease urate secretion into the intestinal lumen. In the ABCG2 functional subgroup analysis, the uric acid concentrations at baseline in the 100%, 75%, and 50% functional ABCG2 groups were 105.3 pg/

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μL (IQR: 12.3–236.6), 113.0 pg/μL (IQR: 9.4–258.0), and 70.1 pg/μL (IQR: 25.5–110.9), respectively. The subgroup analysis showed that the ΔC_{UA} in the 100%, 75%, and 50% functional ABCG2 groups was +175.6 pg/μL/5 min (IQR: 92.6–550.7), +125.9 pg/μL/5 min (IQR: 7.7–476.4), and +65.9 pg/μL/5 min (IQR: −35.1–114.0), respectively (p for trend = 0.058) (Fig. 2). Our previous study demonstrated a negative correlation between SUA and ABCG2 function in patients with end-stage renal disease (ESRD), whose urate excretion pathway is exclusively intestinal [3]. The association between SUA and ABCG2 in patients with ESRD supports our direct observation that ABCG2 is highly involved in intestinal urate secretion. The major *ABCG2* dysfunctional SNP, p.Q141K, is widespread in many ethnic groups and particularly common in Asian populations [29.1% in East Asians, 32.2% in other Asians, and 10.3% in European populations; browsed Allele Frequency Aggregator, https://www.ncbi.nlm.nih.gov/snp/rs2231142, ver.20230706150541)]. Given the high frequenc y of dysfunctional *ABCG2* SNPs, our results present the possibility that decreased uric acid secretion in the intestine due to the SNPs contributes to SUA variability in the general population.

We acknowledge the limitations of our study regarding potential confounders and generalizability. First, our results were estimated using a small sample size, and background factors (e.g., age and sex) were not considered. Second, to avoid unnecessary invasion, our study included individuals who required endoscopy of the small intestine. Although intestinal fluid was collected from normal small intestinal segments without lesions, the effects of inflammation, lesions at other sites, and treatments in patients with Crohn's disease were not considered in our analysis. Finally, the double balloon prevented fluid traffic on the anorectal side but not the oral side. Although the intestinal fluid was collected from an area where the intestinal flexure on the oral side was strong and fluid traffic was almost negligible, the possibility of intestinal fluid traffic on the oral side could not be completely ruled out.

In conclusion, we demonstrated, for the first time, that urate was secreted in the intestine of humans and regulated by ABCG2. ABCG2 causes the excretion of a variety of substances, including toxins (e.g., indoxyl sulfate) and urate, owing to its broad substrate specificity [5]. Therefore, the intestine is an excretory organ that may play an important role in the regulation of urate excretion and the dynamics of other substances.

Table 1 Clinical data and ABCG2 functionality based on two variants [rs72552713 (p.Q126*) and rs2231142 (p.Q141K)].

Subject No.	Age/Sex	ABCG2			Diagnosis	Medication	CRP	SUA	eGFR	C_{UA} in intestinal fluid (baseline/after 5 min)
		rs72552713	rs2231142	Function						
1	39/M	wild type	wild type	100%	Crohn's disease (Location*: L1)	Filgotinib	0.55	5.8	88	1305/3466
2	43/M	wild type	heterozygous	75%	Crohn's disease (Location*: L3)	Infliximab	0.21	5.0	76	n.d./1259
3	68/F	wild type	heterozygous	75%	OGIB	Untreated	0.05	3.3	86	25/525
4	31/M	wild type	heterozygous	75%	Crohn's disease (Location*: L3)	Infliximab	0.05	5.0	74	249/292
5	33/M	wild type	heterozygous	75%	OGIB	5-ASA	0.05	2.7	93	10/18
6	24/M	wild type	homozygous	50%	Crohn's disease (Location*: L3)	Ustekinumab	0.07	7.1	101	6/72
7	43/M	wild type	heterozygous	75%	Crohn's disease (Location*: L3)	Infliximab	0.04	4.0	84	180/415
8	40/M	wild type	wild type	100%	Crohn's disease (Location*: L3)	Adalimumab	0.2	4.9	88	237/336
9	27/M	wild type	homozygous	50%	Crohn's disease (Location*: L3)	Infliximab	0.14	4.4	109	115/n.d.
10	25/M	wild type	heterozygous	75%	Crohn's disease (Location*: L2)	5-ASA	0.04	5.3	154	596/743
11	37/M	wild type	wild type	100%	Crohn's disease (Location*: L1)	Ustekinumab	0.01	7.5	70	129/302
12	36/F	wild type	heterozygous	75%	Simple Ulcer	Untreated	0.06	4.2	82	530/530
13	65/F	wild type	heterozygous	75%	Crohn's disease (Location*: L3)	Infliximab	0.14	3.5	76	132/203
14	49/M	wild type	wild type	100%	Crohn's disease (Location*: L1)	Untreated	1.13	8.9	81	91/2507
15	34/M	wild type	wild type	100%	Crohn's disease (Location*: L1)	Adalimumab	0.05	6.3	85	797/1329
16	73/M	wild type	wild type	100%	Crohn's disease (Location*: L1)	Vedolizumab	0.86	5.3	68	n.d./361
17	34/F	wild type	heterozygous	75%	Crohn's disease (Location*: L3)	Vedolizumab	0.04	3.7	79	n.d./276
18	56/M	heterozygous	wild type	50%	Crohn's disease (Location*: L1)	Adalimumab	1.12	6.5	63	70/205
19	58/M	wild type	heterozygous	75%	Crohn's disease (Location*: L1)	5-ASA	0.16	4.7	99	1276/1122
20	55/M	wild type	wild type	100%	Crohn's disease (Location*: L1)	Ustekinumab	0.38	5.1	72	113/664
21	76/M	wild type	heterozygous	75%	Crohn's disease (Location*: L1)	Infliximab Azathioprine	0.04	5.0	76	176/907
22	47/M	wild type	heterozygous	75%	Simple Ulcer	Untreated	0.17	4.8	98	173/685
23	49/M	wild type	heterozygous	75%	Crohn's disease (Location*: L1)	Infliximab	0.13	7.0	64	7/76
24	41/M	wild type	heterozygous	75%	Crohn's disease (Location*: L3)	Infliximab	0.05	6.5	77	285/753
25	43/M	wild type	wild type	100%	Crohn's disease (Location*: L1)	Adalimumab	0.04	5.2	83	105/87
26	36/M	wild type	heterozygous	75%	Crohn's disease (Location*: L3)	Adalimumab	0.06	6.3	65	94/198
27	21/M	wild type	heterozygous	75%	Crohn's disease (Location*: L3)	Infliximab	0.06	6.4	101	79/282
28	22/M	wild type	wild type	100%	Crohn's disease (Location*: L3)	Predonisolone Azathioprine	0.75	5.3	118	3/63
29	41/M	wild type	homozygous	50%	Crohn's disease (Location*: L1)	Adalimumab	0.07	7.5	81	107/199

Table 1 (continued)

Subject No.	Age/Sex	ABCG2			Diagnosis	Medication	CRP	SUA	eGFR	C_{UA} in intestinal fluid (baseline/after 5 min)
		rs72552713	rs2231142	Function						
30	45/M	wild type	wild type	100%	Crohn's disease (Location*: L3)	Infliximab	0.13	7.9	60	18/110
31	51/M	wild type	wild type	100%	Crohn's disease (Location*: L1)	Ustekinumab	0.04	5.5	85	12/188
32	66/M	wild type	heterozygous	75%	Crohn's disease (Location*: L1)	Adalimumab	0.04	5.3	76	10/16
33	25/M	wild type	homozygous	50%	Crohn's disease (Location*: L1)	Infliximab	0.04	8.2	80	45/90
34	23/F	wild type	heterozygous	75%	Crohn's disease (Location*: L1)	Ustekinumab	0.04	3.9	97	6/10

Abbreviations: ABCG2, adenosine trisphosphate binding cassette subfamily G member 2; CRP, C-reactive protein (mg/dL); SUA, serum urate (mg/dL); eGFR, estimated glomerular filtration rate (mL/min/1.73 m^2); C_{UA}, uric acid concentration (pg/μL); OGIB, obscure gastrointestinal bleeding; 5-ASA, 5-aminosalicylic acid; n.d., not detected. *Locations are listed according to the Montreal classification of Crohn's L1, ileal; L2, colonic; L3, ileocolonic; L4, isolated upper extremity disease

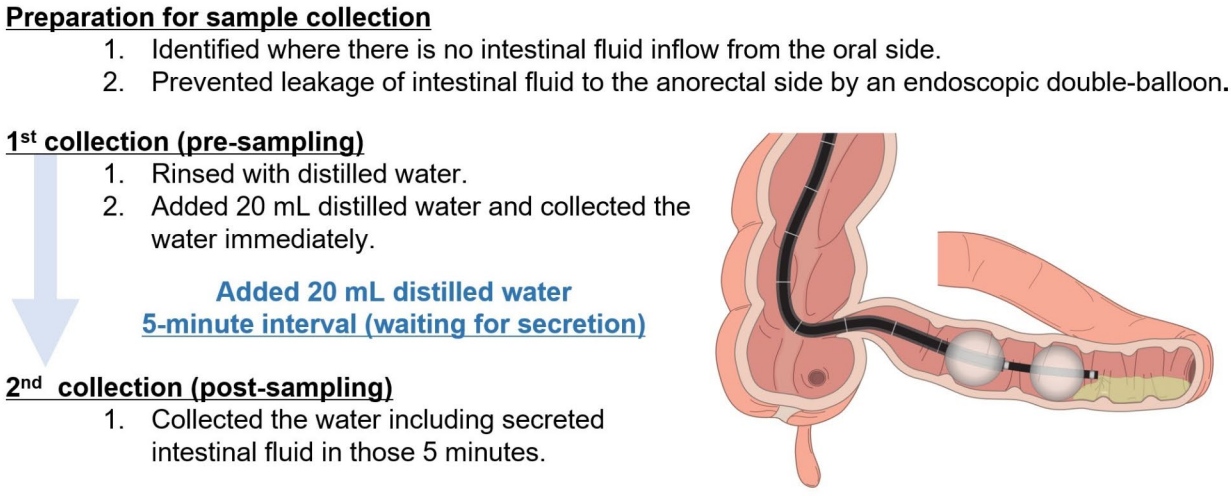

Fig. 1 Procedure for small intestinal fluid sampling

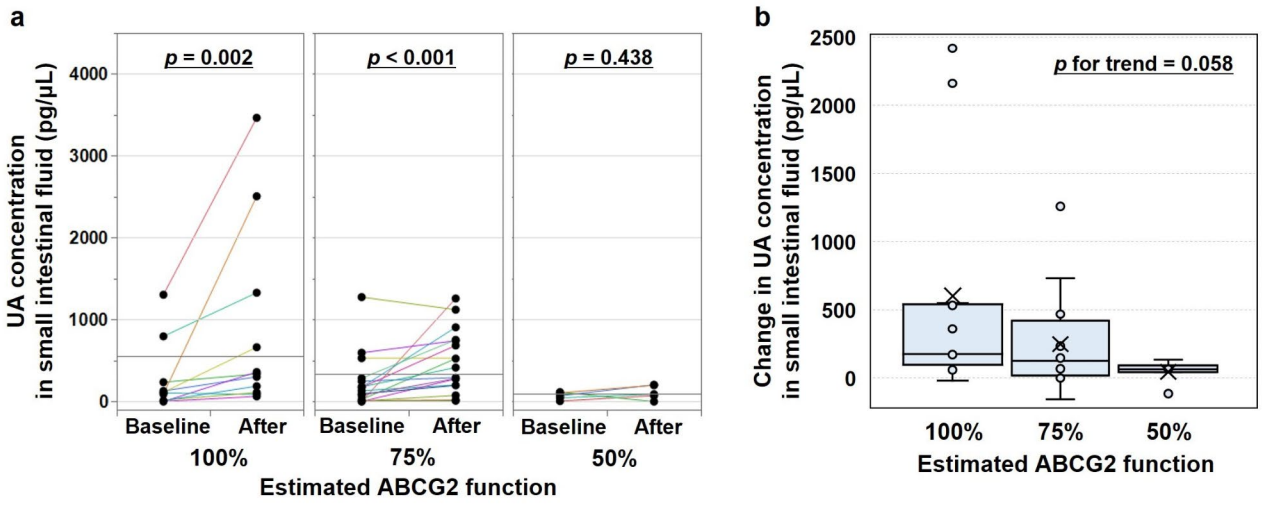

Fig. 2 Relationship between intestinal urate secretion and estimated ABCG2 function. (**a**) The uric acid concentration in the intestinal fluid at baseline and after 5-min intervals. (**b**) The change in uric acid concentration in the intestinal fluid during 5-min intervals. The means of change in uric acid concentration were indicated by ×: 600.5 pg/μL, 249.1 pg/μL, and 44.8 pg/μL in the 100%, 75%, and 50% functional ABCG2 groups, respectively

Abbreviations

ABCG2	Adenosine trisphosphate binding cassette subfamily G member 2
ESRD	End-stage renal disease
IQR	interquartile range
SNP	Single nucleotide polymorphism
SUA	Serum urate
ΔC_{UA}	Change in uric acid concentration in the intestinal fluid

Supplementary Information

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Supplementary Material 1

Supplementary Material 2

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Author contributions
MS designed the study. RM, YO, TS, TI, KI, and MS acquired, analyzed, and interpreted the data. RM, YO, KI, and MS drafted the manuscript. All authors critically reviewed the manuscript, approved the final version to be published, agreed to be personally accountable for the individual's own contributions, and ensured that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, were appropriately investigated and resolved, including documentation in the literature, if appropriate.

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Data availability
The datasets generated or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by the Institutional Review Board Committee of Jikei University School of Medicine (#31-0229521) and Tokyo University of Pharmacy and Life Sciences (#19 – 03). Written informed consent was obtained from all participants prior to their participation, and they could opt out at any point during the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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References

1. Sorensen LB. Role of the intestinal tract in the elimination of uric acid. Arthritis Rheum. 1965;8:694–706.
2. Ichida K, Matsuo H, Takada T, Nakayama A, Murakami K, Shimizu T, et al. Decreased extra-renal urate excretion is a common cause of hyperuricemia. Nat Commun. 2012;3:764.
3. Ohashi Y, Toyoda M, Saito N, Koizumi M, Kanai G, Komaba H, et al. Evaluation of ABCG2-mediated extra-renal urate excretion in hemodialysis patients. Sci Rep. 2023;13:93.
4. Mendez-Salazar EO, Martinez-Nava GA. Uric acid extrarenal excretion: the gut microbiome as an evident yet understated factor in gout development. Rheumatol Int. 2022;42:403–12.
5. Takada T, Yamamoto T, Matsuo H, Tan JK, Ooyama K, Sakiyama M, et al. Identification of ABCG2 as an exporter of uremic toxin indoxyl sulfate in mice and as a crucial factor influencing CKD progression. Sci Rep. 2018;8:11147.

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