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A genome-wide study on gene–nutrient interactions for hyperuricemia in a large Korean cohort (KoGES)

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This study aimed to identify novel genetic variants associated with hyperuricemia risk across multiple nutrients by assessing significant gene–nutrient interactions using large-scale genome-wide association study (GWAS) data in the Korean population. A total of 48,007 individuals from the Korean Genome and Epidemiology Study dataset were included in the GWAS. Dietary intake was evaluated using a food frequency questionnaire. To identify genomic loci that interact with specific nutrients influencing hyperuricemia risk, we conducted a GWAS followed by gene–nutrient interaction analyses of genome-wide significant single-nucleotide polymorphisms (SNPs). Two SNPs with significant gene–nutrient interactions for specific nutrients were identified: rs113206751 in the Membrane-Associated Ring-CH-Type Finger 1 (*MARCH1*) gene and rs9393235 in the Neuroblastoma-Associated Transcript 1 (*NBAT1*) gene near the prolactin (*PRL*) gene. Among individuals consuming vitamin A above the dietary reference intake (DRI), carriers of the minor allele (A) at *MARCH1*-rs113206751 had a higher risk of hyperuricemia than those with the reference allele (-, no insertion) (odds ratio [OR] 1.63, 95% confidence interval [CI] 1.38–1.93, p: 1.01×10^{-8}, interaction p: 1.22×10^{-6}). Among individuals consuming potassium above the DRI, carriers of the minor allele (G) at *NBAT1/PRL*-rs9393235 showed an increased risk of hyperuricemia than those with the reference allele A (OR 3.14, 95% CI 2.09–4.71, p: 3.69×10^{-8}, interaction p: 1.21×10^{-5}). These findings suggest potential gene–nutrient interactions between *MARCH1* and vitamin A, as well as between *NBAT1/PRL* and potassium, in relation to hyperuricemia risk. However, these findings may have limited generalizability beyond the Korean population studied and require validation in more diverse populations. This study emphasizes genomic-nutritional integration for personalized hyperuricemia management.

Keywords Hyperuricemia, Uric acid, Gout, Nutrients, Genome-wide association study

Hyperuricemia, defined as elevated serum uric acid (SUA) levels, plays a critical role in the pathogenesis of gout and is further associated with a variety of clinical conditions such as hypertension (HTN), cardiovascular disease, chronic kidney disease (CKD), obesity, insulin resistance (IR), type 2 diabetes mellitus (DM), and metabolic syndrome[1,2]. Globally, the prevalence of hyperuricemia is estimated to be 2.0–32.1%, with higher rates in men than in women; in Korea, this is reported to be 11.4% overall, 17.0% in males, and 5.9% in females[1,3].

SUA levels are regulated by the balance between hepatic urate production and urate excretion through the kidneys and intestines[4]. Hyperuricemia can result from either increased urate production (often due to excessive purine intake) or reduced excretion[5]. Both genetic and environmental factors contribute to the maintenance of this balance. Several genome-wide association studies (GWASs) have identified genetic loci associated with

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SUA levels and gout[1,6–11], and recent meta-analyses have identified over 351 loci linked to SUA levels[11]. Despite these findings, these genetic variants collectively explain only 7% of the variation in SUA levels, while heritability estimates suggest that genetic factors account for 40–73% of the SUA level variability[12–14]. This discrepancy underscores the need for further research to identify additional genetic and epigenetic factors that contribute to SUA regulation.

The interaction between genetic and environmental factors is a key feature in the development of complex diseases, including hyperuricemia and gout[15]. Among the major environmental factors, diet is a prominent risk factor for the development of various metabolic diseases, including hyperuricemia and gout. Therefore, examining the combined effects of genes and dietary intake can provide additional insights into gene-nutrient interactions and the development of hyperuricemia. A previous study on gene–diet interactions suggested that the interaction between consumption of sugary drinks and SLC2A9 variants is involved in the pathogenesis of gout[16]. Another study reported that the combination of alcohol consumption and carrying the risk allele of *ABCG2* rs2231142 (G > T) significantly increased the risk of developing hyperuricemia compared with carrying the risk allele alone[17].

Although some studies have examined the interaction between specific genetic variants and dietary intake in relation to hyperuricemia, few have focused on the interactions between a broader range of nutrient intake, including micronutrients, and the entire genome. Therefore, the present study aimed to assess participants' intake of various nutrients—including macronutrients and micronutrients—using data from the large-scale Korean Genome and Epidemiology Study (KoGES), and to comprehensively evaluate genetic variants and gene–nutrient interactions associated with hyperuricemia through GWAS analyses. The final objective was to identify novel, previously unreported, gene–nutrient interactions that may contribute to the development of hyperuricemia.

Methods

Study population

The KoGES is a government-funded genome epidemiological research platform that has been established to investigate the genetic and environmental etiology of common chronic diseases in the Korean population (National Research Institute of Health, Korea Disease Control and Prevention Agency, and the Ministry of Health and Welfare). KoGES Health Examination, a subset cohort of the KoGES, enrolled community residents and individuals aged ≥ 40 years, recruited from the National Health Examinee Registry at baseline. The KoGES dataset included data obtained from 58,701 participants with available genome-wide single-nucleotide polymorphism (SNP) genotype information. Detailed information on the KoGES has been provided in a previous study[18]. We excluded 10,045 individuals with a history of cancer or gout or missing data regarding cancer or gout history and 649 individuals with incomplete covariate or measurement data. Finally, 48,007 participants were included in the GWAS and subsequent analyses and categorized into hyperuricemia ($n = 2,05$) and control ($n = 45,202$) groups. Hyperuricemia was defined as SUA level > 7.0 mg/dL (416.0 μmol/L) in males and > 6.0 mg/dL (357.0 μmol/L) in females[3]. Figure 1 shows the flowchart of participant inclusion in the study population. The study protocol adhered to the principles of the 1975 Declaration of Helsinki, and all participants provided informed consent prior to the study. The Institutional Review Board of Theragen Bio (Seongnam, Korea) approved the study protocol (approval number: IRB 4-2024-0575).

Genotyping

This dataset included a wide array of phenotypic and environmental measurements; genome-wide genotyping data; biological samples such as DNA, plasma, serum, and urine; and links to health and administrative records. Blood DNA samples were collected according to standard procedures, transferred to the National Biobank of Korea, and preserved for future studies. Genomic DNA was extracted from peripheral blood samples and subsequently genotyped using the Korea Biobank Array (KoreanChip). Comprehensive details about KoreanChip have been described previously[19].

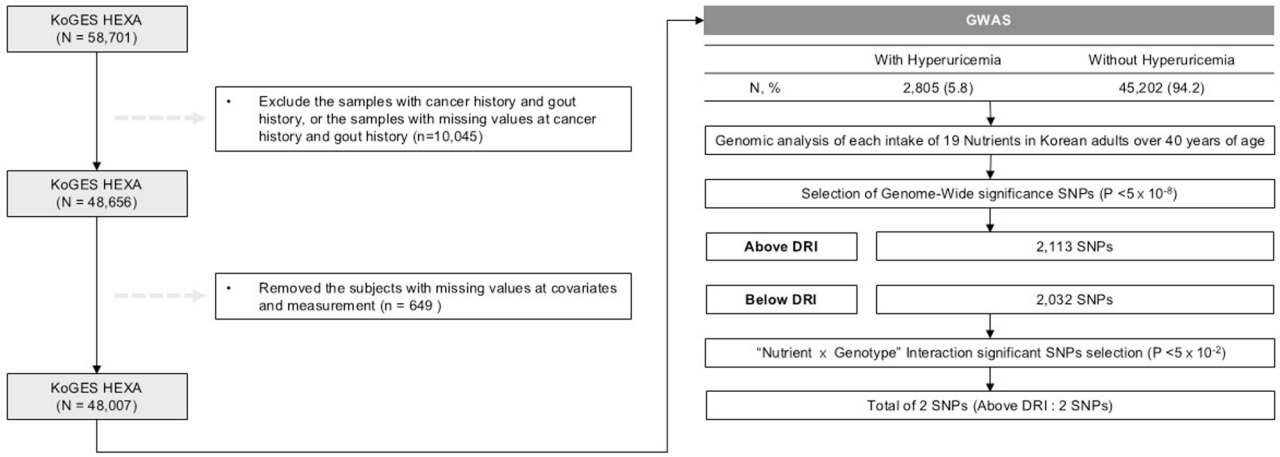

Fig. 1. Flow chart of study design.

Clinical measurements and definition of lifestyle factors

Anthropometric measurements were performed by well-trained medical staff using a standard protocol. Body mass index (BMI) was calculated by dividing the weight (kg) by height squared (m^2). Waist circumference (WC) was measured at the midpoint between the lowest rib and the top of the iliac crest. Blood samples were collected by trained medical staff after the participants underwent 8 h of fasting. Lifestyle data were collected by trained interviewers using questionnaires. Participants were enquired about their drinking status (never, former, or current drinker), and current drinkers were enquired about their drinking habits over the past year. Alcohol consumption (g/day) was estimated based on the frequency, type, and content of alcoholic beverages consumed, and number of drinks per occasion. Smoking status was categorized as never, former, or current smoker. In the questionnaire, regular exercise was defined as at least 30 min of physical activity per day. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured at least twice in the sitting position. HTN was defined as SBP ≥ 140 mmHg, DBP ≥ 90 mmHg, or a history of HTN[20]. DM was defined as fasting serum glucose (FPG) ≥ 126 mg/dL, glycated hemoglobin A1c (HbA1c) ≥ 6.5%, or a history of DM[21]. Hypercholesterolemia, hypertriglyceridemia, and hypo-high-density lipoprotein (HDL) cholesterolemia were defined as total cholesterol (TC) levels ≥ 240 mg/dL, triglyceride (TG) levels ≥ 200 mg/dL, and HDL cholesterol (HDL-C) levels < 40 mg/dL in males and < 50 mg/dL in females[22]. According to the criteria established by the Korean Society for the Study of Obesity, obesity was defined as a BMI ≥ 25 kg/m^2, and abdominal obesity was defined as a waist circumference WC ≥ 90 cm in men and ≥ 85 cm in women[23]. Metabolic syndrome was defined as the presence of at least three of the following criteria: (1) abdominal obesity; (2) SBP ≥ 130 mmHg, DBP ≥ 85 mmHg, or the use of antihypertensive medications; (3) FPG ≥ 100 mg/dL or the use of antidiabetic medications or insulin therapy; (4) TG ≥ 150 mg/dL or treatment with lipid-lowering agents; and (5) HDL-C < 40 mg/dL in males and < 50 mg/dL in females[24].

Determination of nutrition intake reference

A semiquantitative food frequency questionnaire (FFQ) consisting of 103 items was developed to assess the routine dietary intake of Korean adults who participated in the KoGES, and the development and validation of the FFQ have been described elsewhere[18,25]. The FFQ serves as an effective tool in large-scale population studies to evaluate the link between diet and chronic diseases. The participants reported details on the frequency and quantity of foods consumed over the previous year. The nutritional intake criteria used in our study were established in accordance with the 2020 Korean Dietary Reference Intakes (KDRIs). The DRI refers to a set of guidelines used to plan and assess the nutrient intake of healthy individuals, with nutrient recommendations that differ according to age and sex. For macronutrients, including carbohydrates, proteins, and fats, the intake reference criteria were based on the upper limit of the acceptable macronutrient distribution range (AMDR) for each macronutrient. The AMDRs for carbohydrates, proteins, and fats were 55–65%, 7–20%, and 15–30%, respectively[26]. The DRIs for sodium, potassium, vitamin E, and fiber were determined based on "Adequate Intake," which represents the recommended average daily nutrient intake, and is derived from either experimentally determined intake level or the estimated average intake considered adequate for maintaining health in a group (or groups) of apparently healthy individuals[27]. The DRI for cholesterol was determined based on chronic disease endpoints, which serve as reference values for intake levels that affect the outcomes of chronic diseases[28]. As cholesterol intake is not specifically addressed in the 2020 KDRIs, reference values established by U.S. and Canadian guidelines were used for cholesterol. The DRIs for other micronutrients were based on the recommended nutrient intake, which represents the average daily intake level sufficient to meet the nutritional requirements of most (97–98%) healthy individuals. The DRIs vary by sex and age, and since all KoGES participants were > 40 years old, we calculated the average DRI for that age group, stratified by sex. The specific DRI criteria used in this study are listed in Supplementary Table 2[29].

Statistical analysis

The data are presented as means ± standard deviations for continuous variables or as numbers and percentages for categorical variables. To compare the hyperuricemia and control groups, an independent two-sample t-test was used for continuous variables, whereas a chi-square test was applied for categorical variables. Principal component (PC) analysis was conducted to reduce genomic bias related to the geographic region of sample collection, with PC1 and PC2 included as covariates in the statistical analyses.

For each of the 19 nutrient groups, intake was categorized as either above or below DRI. We conducted two independent GWASs to identify genomic variants associated with hyperuricemia. The GWAS results were analyzed for both the hyperuricemia and control groups. All GWASs were performed using logistic regression analysis under a genetic additive model with adjustments for age, sex, smoking status, alcohol consumption, exercise status, total energy consumption, PC1, and PC2, using PLINK version 1.9. Prior to GWAS, SNPs with a minor allele frequency (MAF) below 1% and Hardy-Weinberg equilibrium (HWE) p-values less than 1×10^{-5} were excluded to ensure robust and reliable results. From the GWAS results, we selected SNPs with genome-wide significance ($p < 5 \times 10^{-8}$) for each nutrient intake group (above or below DRI). From these SNPs, we further identified uniquely significant SNPs for a single nutrient group. Interaction analyses for hyperuricemia were performed with the selected SNPs using generalized linear models in R statistics (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria). Finally, we identified the SNP that showed a significant gene-nutrient interaction ($p < 5 \times 10^{-2}$) associated with hyperuricemia.

Sensitivity analysis

To further evaluate gene–nutrient interactions associated with hyperuricemia, we conducted additional sensitivity analyses focusing on the interactions between rs113206751 and vitamin A intake, and rs9393235 and potassium intake. Three complementary approaches were applied. First, a GWAS stratified by nutrient

intake tertiles was performed, categorizing participants into three groups based on intake levels. Genetic associations with hyperuricemia were assessed within each group using logistic regression models adjusted for age, sex, smoking status, alcohol consumption, physical activity, total energy intake, and the first two principal components (PC1 and PC2). Second, generalized linear models (GLMs) incorporating tertile-based nutrient intake groups were used to evaluate gene–nutrient interaction effects on hyperuricemia. Lastly, GLMs treating nutrient intake as a continuous variable were used to further assess interaction effects.

Results

Figure 1 illustrates the overall study design. Hyperuricemia, considered a risk factor for gout and various metabolic disorders, was the outcome of interest, and 19 principal nutrients assessed in the KoGES were analyzed as dietary exposures. Based on the initial GWAS analysis of the included participants, a total of 4145 SNPs were identified as significantly associated with hyperuricemia risk in relation to nutrient intake categorized as either above or below the DRI: 2113 SNPs were associated with intake above the DRI, and 2,032 SNPs with intake below the DRI. Among these SNPs, we identified two that demonstrated significant gene-nutrient interactions in only one direction, either above or below the DRI for a specific nutrient.

Table 1 presents the general characteristics of the study population based on the hyperuricemia status. The mean age of the overall population was 53.55 ± 8.01 years, with 34.7% being male. Participants with hyperuricemia were older than those in the control group. The hyperuricemia group exhibited a higher proportion of males and current or former drinkers and a significantly greater alcohol consumption (188.04 ± 263.36 g/week) compared to the control group (114.27 ± 237.48 g/week). It also demonstrated significantly higher levels of SBP, DBP, BMI, WC, glucose, HbA1c, blood urea nitrogen, creatinine, and c-reactive protein levels than the control group. Additionally, TC, TG, aspartate aminotransferase, alanine aminotransferase, and γ-glutamyl transpeptidase levels were substantially higher in the hyperuricemia group. The prevalences of HTN, DM, hypercholesterolemia, hypertriglyceridemia, hypo-HDL cholesterolemia, metabolic syndrome, myocardial infarction, and ischemic stroke were higher in the hyperuricemia group. Specifically, prevalences of hypertriglyceridemia, metabolic syndrome, obesity, and abdominal obesity were substantially higher in the hyperuricemia group. The mean SUA levels in the hyperuricemia and control groups were 7.43 ± 0.88 and 4.49 ± 1.05 mg/dL, respectively. The hyperuricemia group consumed more calories than the control group, although the mean difference was minimal (approximately 27 kcal/d). The hyperuricemia group had a significantly higher daily intake of proteins (%) and lower intake of carbohydrates (%) and fiber than the control group. Additionally, the hyperuricemia group consumed more fats, phosphorus, vitamin A, sodium, and cholesterol and less calcium, potassium, vitamin C, and folate than the control group, although these differences were not statistically significant. Supplementary Table 1 provides the general characteristics of the study population stratified by sex. Supplementary Table 2 presents the proportions of participants whose intake levels for the 19 nutrients were above or below the DRI. The nutrient intake criteria were set in a sex-specific manner.

Following an initial GWAS analysis of nutrient intake and prevalence of hyperuricemia, nine variants were identified as significant in relation to nutrient intake. Among these, seven variants exhibited broad significance across multiple nutrients, whereas two variants were identified as uniquely significant for specific nutrient intake, with unidirectional significance in intake above the DRI: one variant related to vitamin A and the other related to potassium (Supplementary Table 4). The results of the two significant GWASs are depicted in Fig. 2 as Miami plots using log10 transformed p-values. The significant variant associated with hyperuricemia-vitamin A was rs113206751 (4q32.3) (Fig. 2A), whereas the significant variant associated with hyperuricemia-potassium was rs9393235 (6p22.3) (Fig. 2B). Figure 3 shows the regional association plot for the novel SNPs of rs113206751 and rs9393235. The SNP rs113206751 is located in an intron of the Membrane-Associated Ring-CH-Type Finger 1 (*MARCH1*) gene (Fig. 3A), whereas rs9393235 is positioned in an intron of the Neuroblastoma-Associated Transcript 1 (*NBAT1*) gene and near the Prolactin (*PRL*) gene (Fig. 3B). The entire GWAS and gene–nutrient interaction analyses are detailed in Supplementay Tables 3 and 4.

Table 2 presents the odds ratios (ORs) for hyperuricemia prevalence by genotype and nutrient intake level, along with the gene-nutrient interaction p-values for the two SNPs that exhibited significant nutrient-gene interactions associated with hyperuricemia. Among individuals consuming vitamin A above the DRI (737.5 mcg/day for men, 612.5 mcg/day for women), carriers of the *MARCH1*-rs113206751 minor allele (A) showed a higher risk of hyperuricemia than those with the reference allele (-, no insertion) (OR 1.63, 95% confidence interval [CI] 1.38–1.93, p: 1.01×10^{-8}, interaction p: 1.22×10^{-6}). Similarly, among individuals consuming potassium above the DRI (3.5 mg/day for both men and women), carriers of the *NBAT1*/*PRL*-rs9393235 minor allele (G) also showed a higher risk of hyperuricemia than those with the reference allele A (OR 3.14, 95% CI 2.09–4.71, p: 3.69×10^{-8}, interaction p: 1.21×10^{-5}). Among individuals consuming either vitamin A or potassium below the DRI, the risk of hyperuricemia did not differ regardless of allele type. In the subgroup analyses stratified by sex, although stratification resulted in a reduced sample size within each category and a consequent reduction in statistical power in both males and females, the overall trends were consistent with those observed in the non-stratified analysis. Furthermore, the gene–nutrient interactions related to vitamin A and potassium intake were statistically significant in association with hyperuricemia in both males and females (Supplementary Table 5).

The tertile-based approach used for sensitivity analysis reduced the sample size within each category, resulting in decreased statistical power; however, the overall trends were consistent with those observed in the DRI-based dichotomized analysis. In the highest intake groups of vitamin A and potassium, individuals carrying the A1 allele demonstrated a higher risk of hyperuricemia compared to those with the reference allele, although a statistically significant interaction was observed only for the rs113206751–vitamin A interaction ($p = 9.32 \times 10^{-3}$) (Supplementary Table 6). Notably, when nutrient intake was treated as a continuous variable rather than being categorized, statistically significant interactions were observed for both rs113206751–vitamin A ($p = 7.15 \times 10^{-4}$) and rs9393235–potassium ($p = 2.00 \times 10^{-2}$).

	Total	With hyperuricemia	Without hyperuricemia
N	48,007	2805	45,202
Age, years	53.55 ± 8.01	55.17 ± 8.18	53.45 ± 7.98
Male, n (%)	16,650 (34.7)	1839 (65.6)	14,811 (32.8)
Anthropometric traits			
BMI, kg/m^2*	23.89 ± 2.88	25.56 ± 3.07	23.79 ± 2.84
WC, cm*	80.69 ± 8.64	86.7 ± 8.16	80.32 ± 8.53
SBP, mmHg*	122.55 ± 14.86	127.68 ± 14.73	122.24 ± 14.81
DBP, mmHg*	75.54 ± 9.83	78.83 ± 10.07	75.33 ± 9.77
Lifestyle			
Smoking status, n (%)*			
Current	5448 (11.4)	555 (19.8)	4893 (10.8)
Former	7584 (15.8)	895 (31.9)	6689 (14.8)
Never	34,975 (72.8)	1,355 (48.3)	33,620 (74.4)
Drinking status, n (%)*			
Current	21,719 (45.3)	1653 (58.9)	20,066 (44.4)
Former	1649 (3.4)	137 (4.9)	1512 (3.3)
Never	24,639 (51.3)	1015 (36.2)	23,624 (52.3)
Alcohol intake (g/week)*	119.91 ± 240.34	188.04 ± 263.36	114.27 ± 237.48
Exercise status, n (%)#			
Yes	26,158 (54.5)	1596 (57.0)	24,562 (54.3)
No	21,849 (45.5)	1209 (43.0)	20,640 (45.7)
Disease			
HTN (n, %)*	13,885 (28.9)	1413 (50.4)	12,472 (27.6)
DM (n, %)*	4721 (15.2)	410 (20.4)	4311 (14.9)
Hypercholesterolemia (n, %)*	5584 (11.6)	449 (16.0)	5135 (11.4)
Hypertriglyceridemia (n, %)*	6032 (12.6)	842 (30.0)	5190 (11.5)
Hypo-HDL cholesterolemia (n, %)*	13,573 (28.3)	963 (34.3)	12,610 (27.9)
Metabolic syndrome (n, %)*	10,830 (29.6)	1288 (62.6)	9542 (27.7)
Myocardial infarction (n, %)*	1369 (2.9)	149 (5.3)	1220 (2.7)
Ischemic stroke (n, %)*	567 (1.2)	54 (1.9)	513 (1.1)
Obesity (n, %)*	15,486 (32.3)	1,551 (55.3)	13,935 (30.8)
Abdominal obesity (n, %)*	11,040 (23.0)	1187 (42.3)	9853 (21.8)
Biochemical traits			
Glucose, mg/dL*	95.04 ± 19.78	98.95 ± 19.88	94.80 ± 19.74
HbA1c, %*	5.71 ± 0.72	5.83 ± 0.77	5.70 ± 0.72
CRP, mg/dL*	0.14 ± 0.37	0.19 ± 0.33	0.14 ± 0.37
TC, mg/dL*	196.93 ± 35.65	202.04 ± 38.07	196.62 ± 35.47
TG, mg/dL*	125.15 ± 86.01	178.27 ± 121.09	121.85 ± 82.22
HDL-C, mg/dL*	53.98 ± 13.19	48.39 ± 12.02	54.32 ± 13.18
AST (IU/L)*	23.58 ± 24.03	29.43 ± 85.49	23.22 ± 12.46
ALT (IU/L)*	22.16 ± 22.69	30.29 ± 63.60	21.65 ± 17.03
γ-GTP (IU/L)*	30.43 ± 39.95	51.49 ± 60.68	29.12 ± 37.90
BUN (mg/dL) *	14.42 ± 3.93	16.39 ± 5.49	14.30 ± 3.77
Cr (mg/dL)*	0.80 ± 0.20	1.00 ± 0.40	0.78 ± 0.17
Uric acid (mg/dL)*	4.66 ± 1.25	7.43 ± 0.88	4.49 ± 1.05
Nutrients			
Total energy, kcal/day	1738.97 ± 552.18	1764.42 ± 544.51	1737.39 ± 552.63
Protein (%)#	13.35 ± 2.56	13.43 ± 2.67	13.34 ± 2.55
Fat (%)	13.87 ± 5.43	14.06 ± 5.69	13.86 ± 5.42
Carbohydrate (%)#	71.75 ± 7.01	71.39 ± 7.35	71.77 ± 6.99
Ca, mg/day	439.97 ± 254.78	423.1 ± 245.19	441.03 ± 255.33
P, mg/day	882.56 ± 353.17	886.85 ± 350.49	882.31 ± 353.34
Iron, mg/day	9.90 ± 4.86	9.87 ± 4.68	9.9 ± 4.88
Na, mg/day	2404.3 ± 1,369.63	2440.98 ± 1,393.3	2402.08 ± 1,368.12
K, mg/day	2204.69 ± 1,029.06	2182.99 ± 1,020.67	2206.08 ± 1,029.58
Vitamin A (R.E.)	473.87 ± 338.42	475.36 ± 342.7	473.79 ± 338.15
Continued			

	Total	With hyperuricemia	Without hyperuricemia
Vitamin B1, mg/day	0.99 ± 0.44	1.01 ± 0.44	0.99 ± 0.44
Vitamin B2, mg/day	0.89 ± 0.44	0.89 ± 0.43	0.89 ± 0.44
Niacin, mg/day	14.38 ± 6.15	14.74 ± 6.18	14.36 ± 6.15
Vitamin C, mg/day	104.17 ± 66.57	99.09 ± 63.64	104.48 ± 66.74
Zinc, mg/day	7.88 ± 3.57	8.08 ± 3.58	7.86 ± 3.57
Vitamin B6, mg/day	1.57 ± 0.68	1.57 ± 0.68	1.57 ± 0.68
Folate, mcg/day	213.97 ± 118.81	209.81 ± 115.7	214.24 ± 119.0
Fiber, g/day#	5.65 ± 2.80	5.52 ± 2.73	5.66 ± 2.8
Vitamin E, mg/day	8.07 ± 4.39	8.1 ± 4.25	8.07 ± 4.4
Cholesterol, mg/day	168.57 ± 124.85	170.49 ± 125.95	168.46 ± 124.78

Table 1. Characteristics of the study population. BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension; DM, diabetes mellitus; HbA1c, glycated hemoglobin A1c; CRP, C-reactive protein; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; BUN, blood urea nitrogen; Cr, creatinine; Ca, calcium; P, phosphorus; K, potassium; Na, sodium; R.E., retinol equivalents. Data are presented as mean ± standard deviation for continuous variables or number (%) for categorical variables. p-values were calculated using the independent two-sample *t*-test for continuous variables and the chi-squared test for categorical variables, adjusted for age and sex. # $p < 0.05$, * $p < 0.001$.

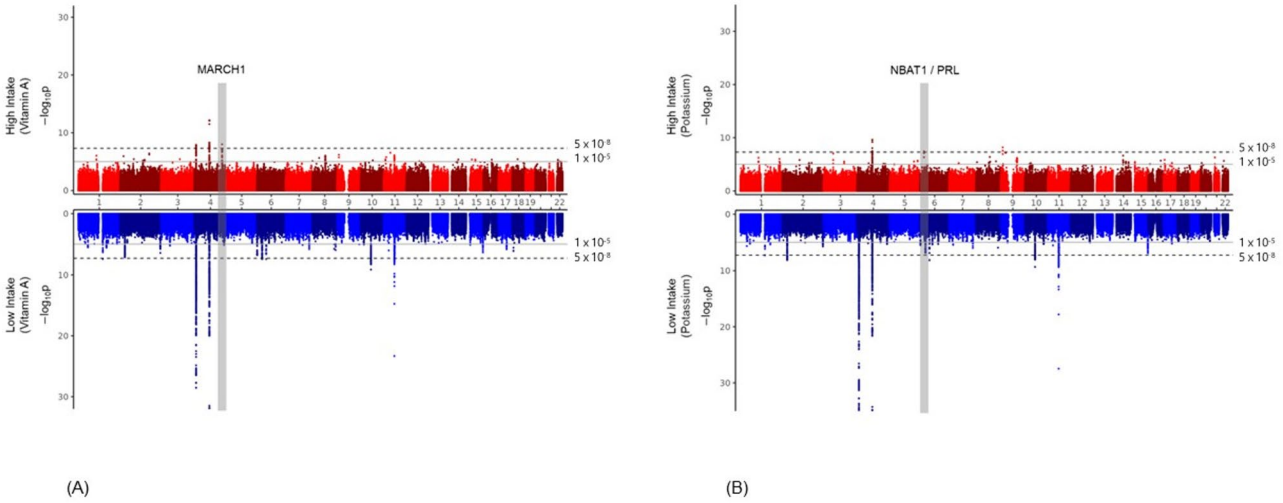

Fig. 2. A Miami plot showing SNP association p-values with hyperuricemia according to specific nutrients. (**A**) SNP rs113206751 associations with hyperuricemia according to vitamin A intake (**B**) SNP rs9393235 associations with hyperuricemia according to potassium intake Genome-wide significant p-value criteria (p 5 × 10-8) are shown by dotted lines, and genome-wide suggestive p-value criteria (p 1 × 10-5) are shown by solid lines. The horizontal axis shows the chromosomal position, whereas the vertical axis shows the p-values transformed into –log10 scale of the SNPs. Candidate genes were identified as those nearest to the lead SNPs, with nearby variant clusters showing similar significance SNP, single nucleotide polymorphism.

Discussion

This study investigated the relationship between nutrient intake, genetic factors, and hyperuricemia, focusing on the impact of gene-nutrient interactions on hyperuricemia risk, using large-scale GWAS data from a Korean population. We identified two SNPs that exhibited significant gene–nutrient interactions in a unidirectional manner, either above or below the DRI for a specific nutrient. Among individuals consuming vitamin A above the DRI, those with the minor allele (A) at the rs113206751 locus of the *MARCH1* gene (4q32.3) showed a 1.63 times higher risk of developing hyperuricemia than those with the reference allele (-, no insertion). Among individuals consuming potassium above the DRI, those with the minor allele (G) at the rs9393235 locus of the *NBAT1* gene (6p22.3) had a 3.14 times higher risk of developing hyperuricemia than those with the reference allele A. These gene–nutrient interactions related to vitamin A and potassium intake remained statistically significant in association with hyperuricemia in both males and females in sex-stratified analyses. This suggests that the observed associations are not restricted to a specific sex, despite well-documented sex-based differences

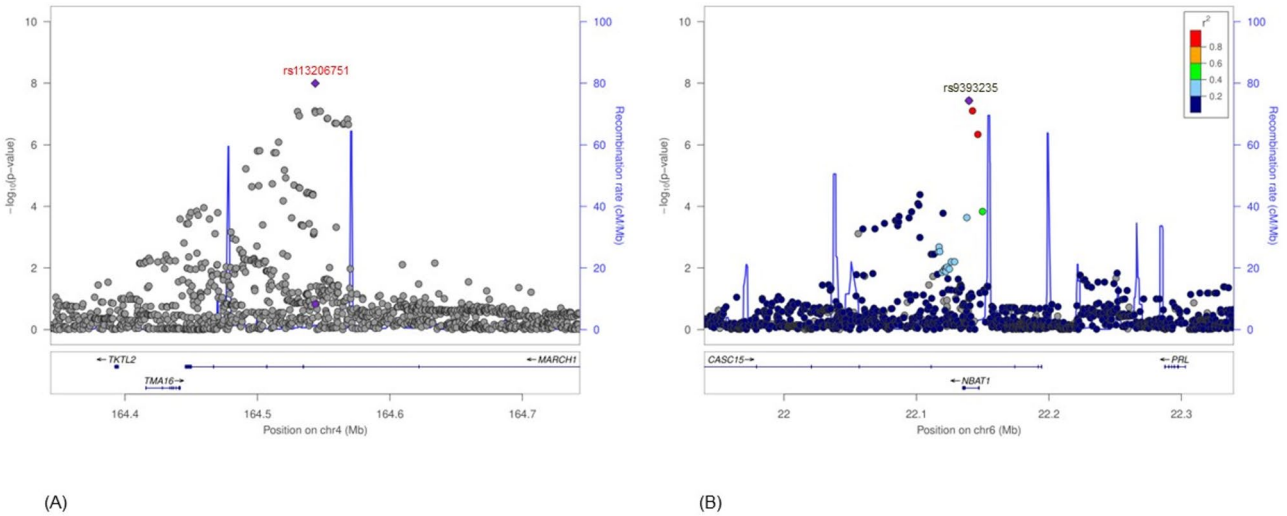

Fig. 3. Signal plot of the novel SNPs with identified gene-nutrient interactions. (**A**) Genomic region around SNP rs113206751 associated with vitamin A intake (**B**) Genomic region around SNP rs9393235 associated with potassium intake. The regional association of lead SNPs identified through gene-nutrient interactions in the GWAS was plotted. The horizontal axis shows the positions of the SNPs on the chromosome, whereas the left vertical axis shows the p-values transformed into –log10 scale. SNP, single nucleotide polymorphism; GWAS, genome-wide association study.

in uric acid metabolism and hyperuricemia prevalence. Among the seven SNPs that exhibited considerable significance for multiple nutrients, the genes (*PDZK1*, *GCKR*, *SLC2A9*, *ABCG2*, *MARCH1*, *BICC1*, and *IGF1R*) corresponding to six SNPs had already been reported to be associated with hyperuricemia risk, supporting the validity of the findings in this study[11,13,30,31].

Vitamin A plays a critical role in the immune system. Vitamin A deficiency can compromise mucosal barrier integrity and decrease the number and/or functional capacity of innate immune cells. Additionally, vitamin A is involved in the final maturation of pre-dendritic cells into mature lymphoid dendritic cells and plays a critical role in regulating adaptive immune responses[32]. A high-vitamin A diet increased interleukin-10 (IL-10) levels while decreasing interferon-γ levels in cultures stimulated with influenza antigens[33]. In another study, IL-10 stimulated the expression of *MARCH1* in activated macrophages[34].

MARCH1, a member of the MARCH family of E3 ubiquitin ligases, is expressed in antigen-presenting cells (APCs), where it plays a key role in downregulating major histocompatibility complex class II molecules and CD86[35,36]. However, basal expression of MARCH1 has also been detected in other cells, indicating that its function extends beyond the ubiquitination of antigen presenting molecules in APCs[36]. Bhagwandin et al. reported that MARCH1 deficiency increases IR by altering the mammalian target of rapamycin (mTOR) signaling and CD8 + T cell metabolic activity in the immune system, related to adipose tissue inflammation[37].

Li et al. reported that MARCH1 plays an important role in the mTOR signaling pathway and acts as a negative regulator of the TANK-binding kinase 1 (TBK1)-mTOR signaling cascade by ubiquitinating TBK1[38]. Vazirpanah et al. reported that mTOR pathway genes are more highly expressed in patients with gout than in healthy controls ($p < 0.0001$) and showed a significant positive correlation between mTOR gene expression levels and SUA levels ($p = 0.014$). Furthermore, in vitro experiments revealed that metformin reduced gout attack rates by inhibiting the mTOR pathway, thereby attenuating inflammasome activity and inflammation[39]. mTOR plays a central role in cellular signaling, and its upregulation is associated with various diseases. It serves as a common pathogenic pathway involved in vascular diseases, inflammation, obesity, progressive kidney disease, and DM[40,41].

Given the aforementioned evidence, MARCH1 has the potential to affect SUA levels by modulating multiple immune signaling pathways. Therefore, a decrease in *MARCH1* expression may upregulate mTOR signaling in the immune system, potentially contributing to increased IR and elevated SUA levels. Vitamin A is involved in immune system development and plays a regulatory role in both cellular and humoral immune responses. Although the immunoregulatory mechanisms of vitamin A are not fully understood, vitamin A, as an immunomodulatory nutrient, may interact with MARCH1, a regulator involved in immune signaling pathways, potentially influencing SUA levels. However, the proposed pathway involving MARCH1-mediated regulation of mTOR signaling and its downstream effects on uric acid metabolism is a mechanistic hypothesis based on existing literature. The functional relevance of rs113206751 in this context has not been directly validated in our study. Further mechanistic investigations are needed to substantiate the proposed interaction.

Potassium, which is abundant in vegetables and fruits, has been reported to exert positive effects on blood pressure and cardiovascular health in epidemiological, clinical, and experimental studies. The Dietary Approaches to Stop Hypertension (DASH)-Sodium trial results demonstrated that the DASH diet, which provides approximately 120 mmol/day of potassium, significantly reduced blood pressure[42]. Furthermore, a

SNP	Chr: BP	REF	ALT	Mapped gene	Consequence	A1	Minor allele frequency				Nutrient intake levels	Association with hyperuricemia		
							This study	Other ethnics				Only genotype		Genotype × nutrient interaction *p*
								EAS	EUR	AMR		OR (95% CI)	*p*	
rs113206751	4:164543594	–	A	*MARCH1*	Intron	A	0.16	0.24	0.04	0.11	Above Vitamin A Below Vitamin A	**1.63 (1.38–1.93)** 1.01 (0.93–1.09)	$\mathbf{1.01 \times 10^{-8}}$ 9.06×10^{-1}	$\mathbf{1.22 \times 10^{-6}}$
rs9393235	6:22139634	A	G	*NBAT1/PRL*	Intron	G	0.03	0.03	0.00	0.00	Above Potassium Below Potassium	**3.14 (2.09–4.71)** 0.92 (0.77–1.11)	$\mathbf{3.69 \times 10^{-8}}$ 4.03×10^{-1}	$\mathbf{1.21 \times 10^{-5}}$

Table 2. SNPs showing significant interactions with nutrients associated with hyperuricemia. SNP, single nucleotide polymorphism; Chr, chromosome; BP, base pair; EAS, East Asian; EUR, European; AMR, American; OR, odds ratio; CI, confidence interval. p-values were calculated using logistic regression analysis adjusted for age, sex, exercise, smoking, alcohol intake (g/day), total calorie consumption, and the first two principal components (PC1 and PC2). The interaction p-values were calculated using the interaction term of the general linear regression model.

post hoc analysis in the DASH-Sodium clinical trial revealed a significant reduction in SUA levels following the consumption of potassium-rich diets, including the DASH and fruit and vegetable diets, compared with the consumption of a non-potassium-rich diet[43]. Potassium predominantly resides inside cells in the body. Because the precise control of intracellular potassium (K+) gradient is essential for life, its distribution and excretion are regulated by multiple integrated systems, including the hormonal actions of insulin, catecholamines, and aldosterone. In addition, potassium excretion by the kidneys plays a critical role in maintaining systemic potassium homeostasis, with potassium being reabsorbed and secreted in the renal tubules[44].

The kidneys also play a critical role in regulating circulating uric acid levels by reabsorbing filtered urate and managing 60–70% of the total uric acid excretion[45]. A previous study investigating the relationship between urinary sodium and potassium excretion and renal uric acid excretion showed that in hypertensive patients with CKD, the fractional excretions of sodium and potassium were positively associated with the fractional excretion of uric acid[46]. The study emphasizes the potential relationship between urinary sodium and potassium excretion and renal uric acid management.

rs9393235 is located on the *NBAT1* gene and is positioned in proximity to the *PRL* gene. *NBAT1* is an RNA gene belonging to the family of long non-coding RNAs, which regulate gene expression, and serves as a biomarker that significantly predicts clinical outcomes in neuroblastoma. Additionally, aberrant *NBAT1* expression is associated with a poor prognosis in several types of cancer[47]. *PRL* is a protein-coding gene that encodes the anterior pituitary hormone prolactin. Prolactin deficiency is associated with metabolic and cardiovascular complications. Krysiak et al. reported that men with hypoprolactinemia exhibited higher SBP and elevated plasma concentrations of cardiometabolic risk factors, including SUA, than men with prolactin levels within the reference range. Furthermore, this study found that normalization of prolactin levels was associated with improvements in biochemical parameters, including SUA levels[48]. In the present study, individuals carrying the minor allele at rs9393235 exhibited higher SUA levels than those with the reference allele, particularly among individuals with potassium intake above the dietary reference level. Although the functional consequences of this variant remain unknown, its location near the *PRL* gene raises the possibility that genetic variation in this region may influence prolactin-mediated regulation of uric acid metabolism.

To date, there is no direct evidence that potassium intake modulates gene expression in this genomic region. However, previous studies have reported that extracellular potassium concentrations and the membrane potential generated by the K^+ gradient induce dopamine release in various regions of the brain[49,50], and prolactin is inhibited by dopamine in the hypothalamus[51]. In summary, extracellular potassium concentrations resulting from higher potassium intake may enhance dopamine release, potentially leading to a reduction in prolactin levels. Additionally, prolactin interacts with dopamine and regulates ion and fluid transport across cell membranes[52,53]. Given these findings, potassium intake may influence the reciprocal regulatory pathway between dopamine release and *PRL* gene expression, potentially influencing SUA levels, a component of cardiometabolic risk factors. Among individuals with potassium intake below the reference level, the presence of the minor allele at rs9393235, located near the *PRL* gene, did not appear to significantly influence the risk of hyperuricemia. However, among those with potassium intake exceeding the reference level, carriers of the minor allele may have experienced a diminished benefit of potassium on SUA levels, potentially contributing to elevated SUA concentrations, despite the generally favorable effects of potassium intake on uric acid metabolism. These observations raise the possibility of a mechanistic link in which potassium intake affects dopaminergic regulation of *PRL* expression, thereby impacting uric acid homeostasis. Nevertheless, this remains a hypothetical interpretation based on existing literature, as no direct causal pathway has been demonstrated linking the functional relevance of rs9393235 to *PRL* gene regulation and SUA metabolism. Further mechanistic studies are needed to validate this potential gene–nutrient interaction.

This study has some limitations. First, it was conducted on Korean adults aged 40–69 years, which limits the generalizability of the findings to other populations and age groups. Additionally, nutrient intake was assessed using the 2020 KDRIs, which reflect the nutritional standards of the Korean population. While appropriate for this study, potential differences in dietary guidelines across countries should be taken into account when interpreting the findings. Second, nutritional data were collected using a semi-quantitative FFQ, which is subject to recall bias and potential reporting inaccuracies. This limitation may affect the precision of nutrient intake estimates. Third, because the study employed a cross-sectional design, causal relationships among nutrient intake, genetic factors, and hyperuricemia could not be established. Longitudinal studies are required to confirm these associations. Fourth, the KoGES dataset lacks information on urate-lowering medication use; thus, individuals with self-reported gout or current treatment were excluded as a proxy. However, the reliance on self-reported data and the inability to identify individuals taking urate-lowering agents for asymptomatic hyperuricemia remain limitations. Finally, although gene–nutrient interactions have been identified, the exact biological mechanisms, particularly those involving *MARCH1* and *NBAT1*/*PRL*, remain unclear. Further experimental studies are required to elucidate these underlying mechanisms.

Despite these limitations, this study has several strengths. Unlike previous studies that focused on a limited set of dietary factors, this study examined a broad range of nutrients, including macronutrients and micronutrients, providing a comprehensive view of gene–nutrient interactions. This study utilized data from the KoGES, a nationally representative cohort of 48,007 participants, which enhances the reliability and statistical power of the findings. Furthermore, interaction analyses were conducted only for SNPs that reached genome-wide significance in the initial GWAS. This selection was based on our aim to identify robust and clinically relevant markers for hyperuricemia diagnosis. These SNPs are not only strongly associated with hyperuricemia but may also be involved in diet-responsive pathways, suggesting pleiotropic effects modulated by nutrient intake. While this approach may have excluded potentially meaningful interactions from SNPs without strong main effects, it enhanced the interpretability and potential diagnostic applicability of our findings.

Conclusion

This study highlights the complex interplay between genetic predispositions and dietary factors in the risk of hyperuricemia. In addition, identifying novel potential gene-nutrient interactions involving *MARCH1* and *NBAT1/PRL* genes underscores the importance of integrating genomic and nutritional data in understanding and managing hyperuricemia. While further research is needed to confirm these findings in diverse populations and elucidate the underlying mechanisms, this study lays the groundwork for personalized dietary recommendations that may help prevent and manage hyperuricemia and its associated complications, such as gout.

Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Author contributions

E.Y.K., J.E.C., J.W.L., J.M.P., Y.H.S., Y.J.K., and K.W.H. contributed to the study conception and design. J.E.C. and K.W.H. contributed to the data acquisition and statistical analysis. E.Y.K., J.E.C., Y.J.K., and K.W.H. interpreted the data and drafted the manuscript. J.W.L., J.M.P., and Y.H.S. contributed to the interpretation of results and wrote the manuscript. All authors critically revised the manuscript, provided final approval, and agreed to be accountable for all aspects of the study, thereby ensuring its integrity and accuracy.

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Declarations

Ethics approval and consent to participate

The study protocol adhered to the principles of the 1975 Declaration of Helsinki and all participants provided informed consent prior to the study. The Institutional Review Board of Theragen Bio approved the study protocol (approval number: IRB 4-2024-0575).

Competing interests

The authors declare no competing interests.

Additional information

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