RESEARCH

Interplay of Mediterranean-diet adherence, genetic factors, and metabolic dysfunction-associated steatotic liver disease risk in Korea

Yu-Jin Kwon[1†], Ja-Eun Choi[2†], Kyung-Won Hong[2*] and Ji-Won Lee[3,4*]

Abstract

Backgrounds Metabolic dysfunction-associated steatotic liver disease (MASLD) has gained attention owing to its severe complications. This study aimed to explore the interaction between Mediterranean-diet (MD) adherence, genetic factors, and MASLD risk in a Korean population.

Methods In total, 33,133 individuals aged 40 years and older from the Korean Genome and Epidemiology Study (KoGES) were analyzed. Participants were assessed for MASLD based on criteria and MD adherence measured by the Korean version of the Mediterranean-Diet Adherence Screener (K-MEDAS). Individuals were categorized into two groups based on their MD adherence: high adherence (K-MEDAS > 6) and low adherence (K-MEDAS < 5). Single nucleotide polymorphism (SNP) genotypes were obtained using the Korea Biobank array. Logistic regression was used to examine the single-marker variants for genetic associations with MASLD prevalence.

Results Individuals were categorized into MASLD (10,018 [30.2%]) and non-MASLD (23,115 [69.8%]) groups. A significant interaction was observed between the rs780094 glucokinase regulatory protein (GCKR) gene and K-MEDAS on MASLD ($p < 10^{-2}$). Of individuals with K-MEDAS > 6, those carrying the minor allele (C) of the GCKR gene rs780094 exhibited a lower risk of MASLD compared to those without the allele (odds ratio [OR] = 0.88 [0.85–0.91], p-value = 5.54e^{-13}).

Conclusion The study identified a significant interaction involving the rs780094 variant near the GCKR gene, with carriers of the minor allele exhibiting a lower MASLD risk among those adhering well to the MD. Dietary habits influence the MASLD risk associated with the rs780094 allele, emphasizing the need for personalized nutrition recommendations.

Keywords Mediterranean diet, Metabolic dysfunction-associated fatty liver disease, Gene-diet interaction, Glucokinase regulatory protein gene

†Yu-Jin Kwon and Ja-Eun Choi have co-first authors contributed equally to this work.

*Correspondence:
Kyung-Won Hong
kyungwon.hong@theragenhealth.com
Ji-Won Lee
indi5645@yuhs.ac
Full list of author information is available at the end of the article

Kwon *et al. Journal of Translational Medicine*   (2024) 22:591

Page 2 of 10

Introduction

Over the years, the prevalence of metabolic disorders, such as obesity, metabolic syndrome, and diabetes, has significantly increased in South Korea and globally [1, 2]. This phenomenon results from complex interactions between eating habits, industrialization, changes in social environments, and genetic factors [3]. In particular, the rising incidence of metabolic abnormalities, such as nonalcoholic fatty liver diseases (NAFLD), has raised significant concerns among medical and public health authorities [4]. Recently, the metabolic dysfunction-associated steatotic liver disease (MASLD) concept, which focuses on abnormalities in metabolic function playing a significant role in its etiology, has gained wide acceptance [5]. MASLD is closely associated with metabolic disorders, and it can progress to liver-related complications such as cirrhosis, liver failure, hepatocellular carcinoma, and death [6]. However, the complex pathogenic mechanism underlying the onset and progression of MASLD remains unclear. Recent research has suggested that the complex interplay between genetic variations, lifestyles, and dietary habits may influence the occurrence and progression of MASLD [7].

The Mediterranean diet (MD), a dietary pattern that originates from the Mediterranean region, such as Greece, Spain, and Italy, is characterized by a high intake of vegetables, legumes, fruits, nuts, cereals, and olive oil, with low saturated fat intake and moderate-to-high fish consumption [8]. The MD is well known for preventing heart disease, diabetes, and mortality [8–11]. Several meta-analyses have established that greater adherence to the MD enhances the primary prevention of major chronic diseases, including a significant reduction in mortality, cardiovascular disease, and diabetes [12, 13]. However, these benefits may manifest differently in various population groups with diverse genetic backgrounds and dietary cultures. Therefore, our previous study developed a new MD-adherence questionnaire called the Korean version of the Mediterranean-Diet Adherence Screener (K-MEDAS), which is tailored to the dietary habits of Koreans [14]. Given the large-scale epidemiological nature of this study, we employed K-MEDAS, which is based on a Food Frequency Questionnaire (FFQ), to assess MD adherence among Korean participants. Based on these processes, this study aimed to investigate the role of genetic variations and MD adherence in the prevalence of MASLD using a large prospective cohort of middle-aged Korean adults. To our knowledge, this is the first study to investigate the interplay between MD adherence, MASLD, and genetic factors in the Korean population.

Methods

Study population

This cross-sectional study examines the interplay of genetic and MD diet in prevalent MASLD. This study utilized data from population-based cohorts within the Korean Genome and Epidemiology Study (KoGES), which includes the KoGES_Ansan and Ansung study (a community-based cohort in urban and rural counties), the KoGES_health examinee study (a national health examinee registry), and the KoGES_cardiovascular disease association study (a community-based cohort in rural counties). In the KoGES_Ansan and Ansung study, participants aged 40–69 years voluntarily enrolled at baseline between 2001 and 2002. For the KoGES_health examinee study, participants aged 40 years and over were enrolled at baseline from 2004 to 2013. In the KoGES_cardiovascular disease association study, participants aged 40–69 years were enrolled at baseline from 2005 to 2011.

For baseline recruitment, eligible participants were invited to participate through various methods such as on-site invitations, mailed letters, telephone calls, media campaigns, or community leader-mediated conferences. Those who expressed interest were asked to visit survey sites, comprising more than 50 national and international medical schools, hospitals, and health institutions. At these sites, participants underwent interviews, completed questionnaires administered by trained staff, and underwent physical examinations. The primary reasons for declining participation included changes in contact information (telephone numbers or mailing addresses), being too busy to attend, and not responding to telephone calls [15].

Within the KoGES, 72,299 individuals aged 40 years and older who have genome-wide single nucleotide polymorphism (SNP) genotype data were found. Participants within KoGES who had been diagnosed with liver diseases (n=374), consumed alcohol > 210 g/week in men and 140 g/week in women (n=6.283), had missing data pertaining to laboratory or anthropometric measurements (n=4.778) were excluded. To distinctly investigate the genetic variations based on MD adherence, the participants were stratified into tertile groups based on the Korean version of the Mediterranean-Diet Adherence Screener (K-MEDAS) (T1:< 5; n=13,154, T2: 5 and 6; n=27,731, T3:>6, n=19,979). Subsequently, Genome-Wide Association Studies (GWAS) analysis was exclusively conducted on the upper (top 33.3%) and lower (bottom 33.3%) tertile groups. Therefore, individuals with a K-MEDAS score of 5 or 6 (n=27,731) were also excluded. In total, 33,133 participants were included in the final analysis. Within the lower tertile group (K-MEDAS < 5; n=13,154) a comparison

Kwon *et al. Journal of Translational Medicine*   (2024) 22:591

Page 3 of 10

of SNP differences was conducted between the without (n = 8.631) and MASLD (n = 4.523) participants. Similarly, within the upper tertile group (K-MEDAS > 6; n = 19,979), an analysis of SNP differences was performed between the individuals without (n = 14,484) and with MASLD (n = 5,495).

Informed consent was provided and obtained from all participants in this study. This study was approved by the Institutional Review Board, Theragen Bio (approval number: 700062-220814-GP-007-003).

Assessment of dietary intake and MD adherence

For dietary assessment, a semi-quantitative FFQ was designed, incorporating 103 items, and administered as part of KoGES [16]. Respondents reported the consumption frequency and portion sizes of foods consumed over the preceding year. The analysis of questionnaire data, referencing a food composition database, facilitated the estimation of dietary intakes. Based on the FFQ data, total calories, macronutrient intakes, and micronutrient intakes were estimated.

The K-MEDAS questionnaire, previously developed and validated in a separate study, was employed to assess adherence to the Mediterranean Diet (MD) [14]. Consisting of 14 questions, each scored as either 0 or 1, the K-MEDAS questionnaire yielded a total score ranging from 0 to 14 points. Based on FFQ, foods were categorized to derive a corresponding score for the K-MEDAS. A higher score indicated stronger adherence to the MD. Detailed information about the K-MEDAS questionnaire is provided in the Table S1.

Covariates

Body mass index (BMI) was computed as weight (kg) divided by the square of height (m). Waist circumference (WC) was measured at the midpoint between the lowest rib and the iliac crest. Blood pressures were measured twice using a mercury sphygmomanometer while sitting. Smoking status was classified into three categories: non-smokers, ex-smokers, and current smokers. Alcohol consumption was categorized as non-drinkers (consuming alcohol fewer than 12 times annually, with a single serving not exceeding one cup), ex-drinkers, and current drinkers. Regular exercise leading to perspiration was considered indicative of engagement in physical activity. Participants were requested to fast for at least 8 h before undergoing blood tests. Total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL) cholesterol, blood glucose, glycated hemoglobin (HbA1c), insulin, C-reactive protein (CRP), γ-glutamyltransferase (γ-GGT), aspartate transaminase (AST), and alanine transaminase (ALT) were measured by enzymatic methods using a chemistry analyzer (Hitachi 7600, Tokyo,

Japan by August 2002 and ADVIA 1650, Siemens, Tarrytown, NY from September 2002) according to standardized protocol [15]. Homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as follows: HOMA-IR = (fasting plasma glucose (FPG) in mmol/L × fasting serum insulin in pmol/L) ÷ 22.5 [17]. Hypertension was defined as either a systolic (SBP) or a diastolic blood pressure (DBP) of ≥ 140 mmHg or ≥ 90 mmHg, respectively, or when participants self-reported the diagnosed diseases [18]. Type 2 diabetes was defined as either a fasting blood glucose level of ≥ 126 mg/dL or HbA1c ≥ 6.5% or when participants self-reported the diagnosed diseases [19]. Overweight and obese were defined as BMI ≥ 23 kg/m² and ≥ 25 kg/m², respectively [20].

Assessment of MASLD

A positive diagnosis of MASLD was established based on the presence of blood biomarker evidence of hepatic steatosis and meeting one of the following three criteria: overweight or obesity, the presence of type 2 diabetes, or the presence of at least two metabolic risk abnormalities [21]. Metabolic risk abnormalities are as follows: (1) WC ≥ 90 cm in men and WC ≥ 80 cm in women, (2) SBP ≥ 130 mmHg or DBP ≥ 85 mmHg or drug treatment, (3) TG ≥ 150 mg/dL or drug treatment, (4) HDL-C < 40 mg/dL in men and < 50 mg/dL in women, (5) presence of prediabetes (fasting glucose level 100–125 mg/dL or HbA1c 5.7–6.4%), (6) HOMA-IR score ≥ 2.5, and (7) CRP > 2 mg/dL.

The formula for calculating the Fatty Liver Index (FLI) score is as follows:

$$FLI = [e^{(0.953 \times \ln(TGs) + 0.139 \times BMI + 0.718 \times \ln(\gamma GTP) + 0.053 \times WC - 15.745)}] / [1 + e^{(0.953 \times \ln(TGs) + 0.139 \times BMI + 0.718 \times \ln(\gamma GTP) + 0.053 \times WC - 15.745)}] \times 100$$

[22, 23]. The presence of hepatic steatosis was defined as an FLI > 30 [22, 23].

Genotyping

Fasting blood samples were collected in a one-serum separator tube and two ethylenediaminetetraacetic acid tubes. Blood DNA samples were prepared and transported to the National Biobank of Korea. SNP genotypes were obtained using the Korea Biobank array (KoreanChip), which was specifically designed for the Korean population to facilitate GWAS on blood biochemical traits. The KoreanChip included > 833,000 markers, encompassing over 247,000 rare or functional variants, derived from the sequencing data of over 2,500 Koreans [24]. Detailed information about the KoreanChip can be found in a previous study [24]. Rigorous criteria were applied during KoreanChip data analysis to ensure genotyping quality: a call rate of > 97%, a missing genotype

Kwon *et al. Journal of Translational Medicine*   (2024) 22:591

Page 4 of 10

rate of < 0.01, a minor allele frequency of > 0.01, and a Hardy–Weinberg equilibrium p-value of > 0.000001.

Statistical analysis

Data were presented as mean ± standard deviation or as number (percentages). Continuous variables were evaluated using students' t-tests to compare individuals with and without MASLD, while categorical variables were assessed using Chi-squared tests. Principal component analysis was implemented to mitigate genomic data bias stemming from sample collection regions. Principal component (PC) 1 and PC 2 were included as covariates in subsequent statistical analyses. Logistic regression was applied to examine the single-marker variants for genetic associations with MASLD prevalence, with adjustments for age, sex, BMI, exercise, alcohol, smoking, PC1, and PC2. All statistical analyses were carried out using PLINK software (version 1.07). Significance was determined at $p < 5 \times 10^{-8}$. Values of $p < 5 \times 10^{-2}$ were considered statistically significant for the gene-MD interaction.

Results

Table 1 presents the clinical characteristics of the study population with or without MASLD. Of the total 33,133 study participants, 10,018 (30.2%) had MASLD, while 23,115 (69.8%) did not. Participants with MASLD were more likely to be male and older, with higher levels of BMI, WC, SBP, DBP, fasting glucose, HbA1c, insulin, CRP, HOMA-IR, TC, TG, γ-GGT, AST, ALT, and lower levels of HDL-C. Furthermore, participants with MASLD had a higher proportion of current smokers, current alcohol drinkers, hypertension, and type 2 diabetes, while a lower proportion engaged in regular exercise. Regarding nutritional status, participants with MASLD had a higher total calorie intake and higher intake levels of carbohydrates (g), proteins (g), niacin (mg), zinc (µg), and sodium (mg). Additionally, they had lower intake levels of calcium (mg), iron (mg), potassium (mg), vitamin C (mg), folate (µg), fiber (g), vitamin E (mg), and cholesterol (mg). The mean K-MEDAS score was significantly higher in participants without MASLD compared to those with MASLD.

Table S2 presents the clinical characteristics of the study population without MASLD, categorized by K-MEDAS scores > 6 or < 5. The presentation includes data before and after propensity score matching, with consideration given to age and sex. Of 23,115 study participants, 14,484 (62.6%) had K-MEDAS scores > 6, while 8,631 (37.3%) had K-MEDAS scores < 5. Following propensity score matching, 446 participants each had K-MEDAS scores > 6 and < 5. Table S3 presents the clinical characteristics of the study population with MASLD, categorized by K-MEDAS scores > 6 or < 5. The

presentation also includes data before and after propensity score matching, with consideration given to age and sex. Following propensity score matching, 415 participants each had K-MEDAS scores > 6 and < 5 (Fig. 1).

Table 2 shows the significant SNP with significant association ($p < 10^{-8}$) with MASLD and with significant gene-MD interaction ($p < 10^{-2}$). Of individuals with K-MEDAS > 6, those carrying the minor allele (C) of the glucokinase regulatory protein (GCKR) gene rs780094 exhibited a lower risk of MASLD compared to those not carrying the allele (odds ratio [OR] = 0.88 [0.85–0.91], p-value = $5.54e^{-13}$). However, in individuals with K-MEDAS < 5, a weaker association was observed between rs780094 and MASLD (OR = 0.93 [0.88–0.98], p-value = $5.72e^{-03}$). Regional association plots of the rs780094 are illustrated in Fig. 2.

Supplementary Table 4 presents the SNPs with significant MD scores by gene interaction ($p < 10^{-2}$) associated with MASLD. Forty gene-by-MD score interactions were associated with MASLD. Figure 3 presents a Miami plot showing p values for the SNP associations with MASLD in participants whose K-MEDAS was either < 5 or > 6. We observed genome-wide significant association clusters of GCKR, EIF2B4, IFT172, and ZMAT3 participants with K-MEDAS > 6, and for SEMA3D in participants with K-MEDAS < 5.

We conducted a subgroup analysis based on sex (Table S5). For males, among individuals with a K-MEDAS score greater than 6, those carrying the minor allele (C) of the GCKR gene rs780094 exhibited a lower risk of MASLD compared to those not carrying the allele (OR = 0.80 (0.74–0.88), p-value = $4.4e^{-07}$). Although the p-value was not statistically significant, it indicated a considerable trend toward significance. For females, among individuals with a K-MEDAS score greater than 6, those carrying the minor allele (C) of the GCKR gene rs780094 also exhibited a lower risk of MASLD compared to those not carrying the allele (OR = 0.86 (0.81–0.91), p-value = $6.7e^{-08}$), which was statistically significant. However, in both males and females with a K-MEDAS score below 5, the statistical significance diminished (OR = 0.93 (0.86–1.01), p-value = $6.9e^{-02}$ for male and OR = 0.92 (0.85–0.99), p-value = $3.1e^{-02}$ for female).

Discussion

In this study, we conducted a comprehensive investigation of the interaction between MD adherence, MASLD, and genetic factors within the Korean population. Notably, we identified a significant interaction involving a specific genetic variant, rs780094, located near the GCKR gene region, related to MASLD. We also introduced K-MEDAS as a tool for evaluating MD adherence in the Korean population. Of individuals

Kwon *et al. Journal of Translational Medicine*   (2024) 22:591

Page 5 of 10

Table 1 Clinical characteristics of the study population

Variables	Total	Without MASLD	With MASLD	p-value
N	33,133	23,115	10,018	
Age	54.3 ± 8.3	53.7 ± 8.2	55.7 ± 8.2	< 0.001
Female, n (%)	23,307 (70.2)	18,233 (78.9)	5061(50.5)	< 0.001
BMI, kg/m²	23.9 ± 2.9	22.8 ± 2.2	26.6 ± 2.6	< 0.001
WC, cm	80.7 ± 8.6	77.1 ± 6.8	89.0 ± 6.5	< 0.001
SBP, mmHg	121.9 ± 15.5	119.7 ± 15.1	127.1 ± 15.2	< 0.001
DBP, mmHg	75.5 ± 10.0	74.0 ± 9.7	78.9 ± 9.9	< 0.001
FPG, mg/dL	94.7 ± 19.4	92.1 ± 16.2	100.6 ± 24.3	< 0.001
HbA1c, %	5.7 ± 0.7	5.6 ± 0.6	6.0 ± 0.9	< 0.001
Insulin, IU	7.9 ± 4.2	7.1 ± 3.9	9.0 ± 4.3	< 0.001
HOMA-IR	1.8 ± 1.2	1.6 ± 0.9	2.2 ± 1.5	< 0.001
Hs CRP, mg/dL	0.33 ± 1.63	0.25 ± 1.33	0.53 ± 2.2	< 0.001
TC, mg/dL	197.8 ± 35.9	195.1 ± 34.6	204.1 ± 38.0	< 0.001
HDL-C, mg/dL	52.7 ± 13.1	55.5 ± 13.1	46.1 ± 10.6	< 0.001
TG, mg/dL	125.2 ± 82.4	98.0 ± 46.2	187.6 ± 109.1	< 0.001
γ-GGT, IU/L	26.7 ± 29.5	19.2 ± 13.6	43.4 ± 43.5	< 0.001
AST, IU/L	23.7 ± 15.2	22.2 ± 8.2	27.2 ± 24.2	< 0.001
ALT, IU/L	22.2 ± 19.0	18.8 ± 12.4	30.2 ± 27.3	< 0.001
Current drinking, n (%)	12,510 (37.9)	7.976 (34.7)	4.478 (45.0)	< 0.001
Current smoking, n (%)	3.029 (9.2)	1.432 (6.2)	1.570 (15.8)	< 0.001
Physical activity, n (%)	17,196 (52.0)	12,323 (53.5)	4.845 (45.6)	< 0.001
Hypertension, n (%)	6.745 (20.3)	3.564 (15.4)	3.175 (31.7)	< 0.001
Type2 diabetes, n (%)	2.283 (6.9)	1.210 (5.2)	1.073 (10.7)	< 0.001
Dyslipidemia, n (%)	3.409 (10.3)	1.952 (8.5)	1.454 (14.5)	< 0.001
Mediterranean diet score	6.0 ± 2.2	6.1 ± 2.2	5.8 ± 2.1	< 0.001
Energy, kcal	1746.1 ± 570.2	1733.0 ± 570.6	1776.3 ± 568.3	< 0.001
Protein, g	58.9 ± 26.1	58.6 ± 25.9	59.4 ± 26.8	< 0.001
Fat, g	27.2 ± 17.8	27.2 ± 17.6	27.3 ± 18.3	0.618
Carbohydrate, g	312.5 ± 94.3	309.9 ± 94.9	318.6 ± 92.8	< 0.001
Protein, %	13.3 ± 2.6	13.2 ± 2.6	13.4 ± 2.6	< 0.001
Fat, %	13.5 ± 5.4	13.3 ± 5.4	13.6 ± 5.4	< 0.001
Carbohydrate, %	72.2 ± 6.9	72.4 ± 6.9	72.1 ± 6.9	< 0.001
Calcium, mg	460.2 ± 279.7	467.9 ± 283.2	442.4 ± 270.7	< 0.001
Phosphorus, mg	900.7 ± 375.5	900.7 ± 376.3	900.9 ± 373.6	0.963
Iron, mg	10.2 ± 5.4	10.2 ± 5.4	10.0 ± 5.2	< 0.001
Potassium, mg	2283.2 ± 1129.9	2295.7 ± 1138.1	2255.4 ± 1111.0	< 0.001
Sodium, mg	2521.2 ± 1458.9	2480.4 ± 1423.1	487.3 ± 370.5	< 0.001
Vitamin A, R. E	490.4 ± 368.7	491.8 ± 367.7	2615.5 ± 1533.8	0.317
Vitamin B1, mg	1.00 ± 0.46	1.00 ± 0.45	1.02 ± 0.47	< 0.001
Vitamin B2, mg	0.90 ± 0.46	0.91 ± 0.46	0.90 ± 0.46	0.043
Niacin, mg	14.4 ± 6.3	14.3 ± 6.3	14.6 ± 6.4	< 0.001
Vitamin C, mg	111.4 ± 75.8	113.4 ± 77.0	106.9 ± 73.0	< 0.001
Zinc, μg	7.9 ± 3.7	7.9 ± 3.6	8.0 ± 3.9	0.012
Vitamin B6, mg	1.60 ± 0.73	1.60 ± 0.73	1.60 ± 0.74	0.706
Folate, μg	223.9 ± 131.1	225.6 ± 131.9	220.0 ± 129.3	< 0.001
Fiber, g	6.0 ± 3.2	6.0 ± 3.2	5.9 ± 3.1	0.026
Vitamin E, mg	8.3 ± 4.8	8.3 ± 4.8	8.2 ± 4.7	0.037
Cholesterol, mg	166.9 ± 127.5	169.2 ± 127.7	161.8 ± 127.0	< 0.001

Data are presented as mean ± standard deviations or number (%)

The independent t-test was used to compare continuous variables, while the chi-square test was used to compare categorical variables

Kwon *et al. Journal of Translational Medicine*   (2024) 22:591

Page 6 of 10

Table 1 (continued)

The percentages of energy from carbohydrates, sugars, and proteins were calculated as follows: carbohydrates (g), sugar (g), or protein (g) × 4 kcal/total energy intake (kcal) × 100. The percentages of energy from fatty acids were calculated as follows: fat (g) × 9 kcal/total energy intake (kcal) × 100

MASLD Metabolic dysfunction-associated steatotic liver disease, *BMI* Body mass index, *WC* Waist circumference, *FPG* Fating plasma glucose, *HbA1c* Glycated hemoglobin, *HOMA-IR* Homeostatic Model Assessment for Insulin Resistance, *hsCRP* High-sensitivity C-reactive protein, *TC* Total cholesterol, *HDL-C* High-density lipoprotein cholesterol, *TG* Triglyceride, *r-GGT* r-Glutamyltransferase, *AST* Aspartate transaminase, *ALT* Alanine transaminase

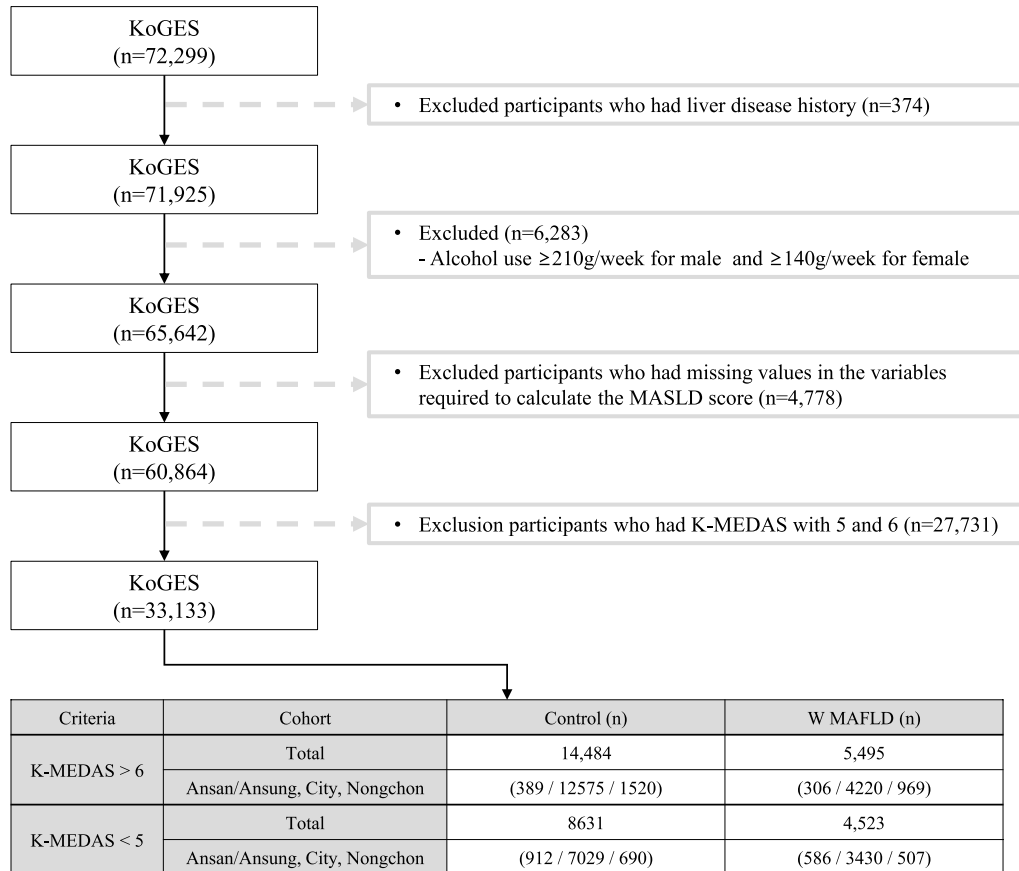| Criteria	Cohort	Control (n)	W MAFLD (n)
K-MEDAS > 6	Total	14,484	5,495
	Ansan/Ansung, City, Nongchon	(389 / 12575 / 1520)	(306 / 4220 / 969)
K-MEDAS < 5	Total	8631	4,523
	Ansan/Ansung, City, Nongchon	(912 / 7029 / 690)	(586 / 3430 / 507)

Fig. 1 Flow chart of study population. *KoGES* Korean Genome and Epidemiology Study, *MASLD* Metabolic dysfunction-associated steatotic liver disease, *K-MEDAS* Korean version of the Mediterranean-Diet Adherence Screener. In total, 33,133 participants (K-MEDAS < 5; n = 13,154 and K-MEDAS > 6; n = 19,979) were included in the final analysis. Within the lower tertile group (K-MEDAS < 5; n = 13,154), a comparison of SNP differences was conducted between participants without (n = 8.631) and with MASLD (n = 4,523). Within the upper tertile group (K-MEDAS > 6; n = 19,979), an analysis of SNP differences was performed between individuals without (n = 14,484) and with MASLD (n = 5.495)

Table 2 Single nucleotide polymorphisms (SNPs) showing significant interactions with K-MEDAS associated with MASLD

SNP	CHR	BP	A1	Gene	ALT	REF	1000 G frequency		
							EAS	EUR	AMR
rs780094	2	27741237	C	GCKR	C	T	0.5238	0.5895	0.6398
	Total		K-MEDAS > 6		K-MEDAS < 5		Genotype x K-MEDAS		
SNP	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	
rs780094	0.88 (0.85–0.91)	$5.5e^{-13}$	0.84 (0.80–0.88)	$5.8e^{-13}$	0.93 (0.88–0.98)	$5.7e^{-03}$	0.91 (0.84–0.99)	1.9^{e-02}	

SNP Single nucleotide polymorphisms, *K-MEDAS* Korean version of the Mediterranean-Diet Adherence Screener, *MASLD* Metabolic dysfunction-associated steatotic liver disease, *Chr* chromosome, *BP* base pair, *EAS* East Asian, *EUR* European, *AMR* American, *N/A* not applicable, *MAF* major allele frequency, *A1* minor allele, *OR* odds ratio, *95% CI* 95% confidence interval
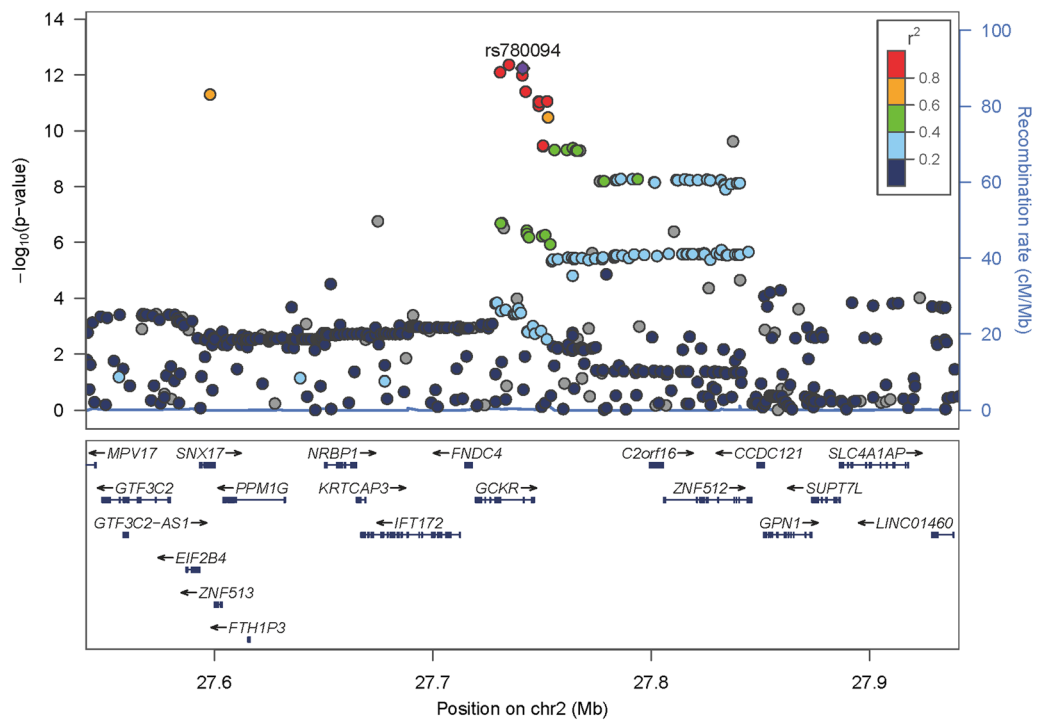
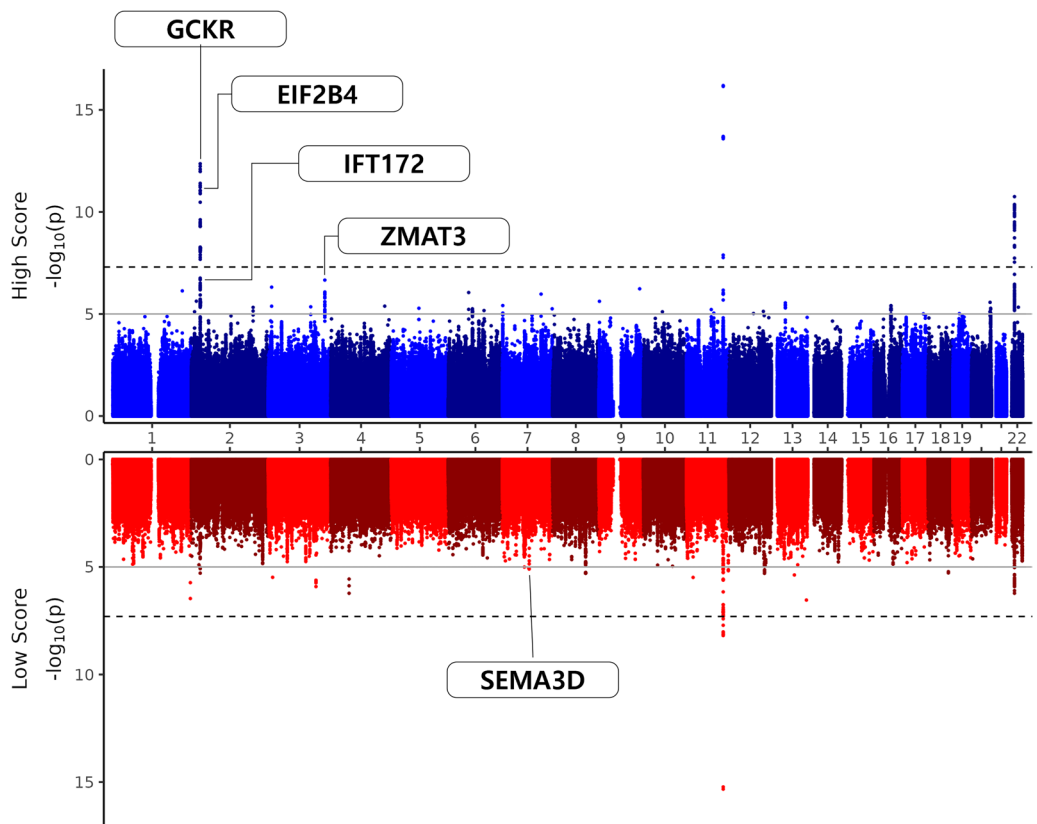**Fig. 2** Regional association plots of the rs780094

Fig. 3 Miami plot showing P values for the SNP associations with MASLD in participants whose K-MEDAS was either < 5 or > 6

Kwon *et al. Journal of Translational Medicine*   (2024) 22:591

Page 8 of 10

with a high MD adherence (K-MEDAS > 6), carriers of the rs780094 minor allele exhibited a 12% lower risk of MASLD compared to those not carrying the SNP (p-value = 5.80E^{-13}). However, among individuals with low MD adherence (K-MEDAS < 5), carriers of the rs780094 minor allele showed a 7% decreased risk of MASLD compared to those not carrying the SNP, though statistical significance was not observed (p-value = 5.72E^{-03}). This suggests that certain genetic factors may modulate the impact of dietary choices on liver health.

The rs780094 variant in the GCKR gene is linked to several health conditions, including type 2 diabetes [25], metabolic syndromes [26], dyslipidemia, and their related traits [27]. Notably, several studies have identified the association between GCKR rs780094 and NAFLD [28, 29].

The GCKR gene, located on chromosome 2 in humans, encodes GCKR, which serves as a key regulator of GCK in the liver [30]. Functional GCKR gene variants affect glucokinase regulatory protein (GKRP) expression, localization, and sequestration ability, resulting in an easier dissociation of GK from GKRP and persistent stimulation of de novo lipogenesis [31]. Regulating GCK expression and activity is a highly intricate process that involves hormonal, metabolic, and environmental factors [32].

GCK, also known as hexokinase (HK) IV, plays a critical role in glucose homeostasis [32]. HK1–3 have high affinities for glucose, and the majority of glucose is processed by these HKs. While GCK has a lower affinity for glucose and is released from GKRP when an excessive amount of glucose enters the cell [32], GCK functions as a glucose sensor in pancreatic beta cells, playing a critical role in glucose-stimulated insulin secretion [33]. Hepatic GCK is modulated at both the transcriptional and post-translational levels [34]. Transcriptional regulation involves the control of GCK gene expression by insulin and glucagon, while post-translational regulation involves the inhibitory action of GCKR on GCK activity.

Two common GCKR variants (rs1260326 and rs780094) have opposing effects on glucose and TG metabolism [30, 35]. The study conducted by Saxena et al. [36] involved the analysis of 386,731 common SNPs in a cohort comprising 1,464 patients with type 2 diabetes and 1,467 matched controls. Their findings revealed that the T allele of the GCKR rs780094 variant is associated with lower levels of fasting glucose and insulin resistance and is correlated with higher levels of plasma TGs [36]. Orho-Melander et al. [35] confirmed that the GCKR rs780094 variant was linked to elevated plasma TG levels and lower levels of FPG. Additionally, they observed that the missense variant rs1260326 (C > T p.P446L), which showed strong linkage disequilibrium (r2 = 0.93) with

rs780094, showed an association with plasma TG levels across 12 independent cohorts [35].

The relationship between the rs780094 variants in the GCKR gene and metabolic status is also influenced by specific dietary patterns [37, 38]. The pronounced interaction observed was between the consumption of whole-grain foods and rs780094 (in GCKR), particularly concerning fasting insulin concentrations [37]. Additionally, n-3 polyunsaturated fatty acids (PUFA) may play a contributing role in triggering insulin resistance and serum levels of CRP by interacting with a rs1260326-P446L genetic variant at GCKR [38].

In this study, of individuals with high MD adherence (K-MEDAS > 6), carriers of the rs780094 minor allele (C) showed a 12% lower risk of MASLD. Unlike previous studies focusing on different racial populations where the T allele was the minor allele, in our Korean study, the rs780094 C allele served as the minor allele. Notably, the overexpression of GKRP in diabetic rats led to enhanced glucose tolerance without triggering hepatic steatosis or elevated plasma TG levels [39]. This suggests the critical regulatory role of GKRP in maintaining a balance in hepatic glucose and lipid metabolism. Many assertions regarding gene-biomarker and gene-disease associations, as documented in published studies, have not been substantiated through replication when examined in independent populations.

In Pollin's study [40], another finding emerged. They did not observe a significant association between either the GCKR SNP or progression to diabetes in the Diabetes Prevention Program. Similarly, intensive lifestyle intervention seems to partially alleviate the impact of the 446L allele on elevated TG levels, while the P446 allele appears to amplify responsiveness to the HOMA-IR-lowering effect of metformin. In our study, of the participants adhering well to the MD, individuals with the rs780094 allele exhibited a lower risk of MASLD. Conversely, no statistical significance was observed in groups with low MD adherence. This suggests that lifestyle modifications may influence the risk of MASLD associated with the rs780094 allele, highlighting the impact of dietary habits on genetic predisposition.

Our study had some limitations. Firstly, it has a cross-sectional design, which precludes the establishment of causal relationships. Secondly, we calculated K-MEDAS based on the FFQ developed by the Korea Centers for Disease Control and Prevention. Moreover, variations in dietary cultures and food choices between Korea and Mediterranean coastal countries can influence the assessment of individuals' MD adherence. Notably, K-MEDAS is an adapted and validated version of an MD adherence screener originally designed for the Mediterranean region. Furthermore, it has been validated as

Kwon *et al. Journal of Translational Medicine*   (2024) 22:591

Page 9 of 10

a reliable tool for assessing MD adherence within the Korean population [14]. Third, we employed an FLI score for diagnosing NAFLD, which may not be as precise as histological confirmation or other advanced imaging modalities. However, in large-scale population-based epidemiological studies, using the FLI score is valuable, and previous research has demonstrated its good accuracy [41, 42]. Forth, blood sampling was conducted after a minimum fasting period of 8 h, which may not be as accurate as the recommended 10–12 h fasting period for lipid profile measurements. Additionally, this study analyzed secondary data from the cohort conducted by the Korea Disease Control and Prevention Agency, making it impossible to obtain specific information regarding the quality control material results. Finally, this study does not comprise a statistically random sample that is representative of the entire population, as is common in many prospective cohort studies. Therefore, it is important to consider these factors when applying the results to the entire population.

Despite these limitations, this study is the first to explore the interplay between MD adherence, genetic factors, and MASLD in a Korean population.

Conclusion

The identified rs780094 gene, located near the GCKR gene region, modified the effects of the MD on the MASLD risk in the Korean population. The results underscore the potential benefits of an MD in reducing MASLD risk, with specific genetic markers modulating these effects. This research provides valuable insights into developing personalized nutrition recommendations and highlights the need for continued investigation into the complex pathogenic mechanisms of MASLD.

Abbreviations

ALT	Alanine transaminase
AST	Aspartate transaminase
BMI	Body mass index
CRP	C-reactive protein
DBP	Diastolic blood pressure
FPG	Fasting plasma glucose
FLI	Fatty liver index
FFQ	Food frequency questionnaire
GWAS	Genome-wide association studies
GCKR	Glucokinase regulatory protein
γ-GGT	γ-Glutamyltransferase
HbA1c	Glycated hemoglobin
HDL	High-density lipoprotein
HOMA-IR	Homeostasis model assessment insulin resistance
K-MEDAS	Korean version of the Mediterranean-diet adherence screener
MD	Mediterranean diet
KoGES	Korean genome and epidemiology study
MASLD	Metabolic dysfunction-associated fatty liver disease
NAFLD	Nonalcoholic fatty liver diseases
SNP	Single nucleotide polymorphism
SBP	Systolic blood pressure
TC	Total cholesterol
TG	Triglyceride
PUFA	Polyunsaturated fatty acids
WC	Waist circumference

Supplementary Information

Author contributions
YJK, JEC, KWH, and JWL contributed to the conception or design of the work. YJK, JEC, KWH, and JWL contributed to the acquisition, analysis, or interpretation of the data and the drafting of the manuscript. All authors critically revised the manuscript, provided final approval, and agreed to be accountable for all aspects of the work, ensuring integrity and accuracy.

Availability of data and materials
Data in this study were from the Korean Genome and Epidemiology Study and are available on the following website: https://www.kdca.go.kr/contents.es?mid=a40504010000

Declarations

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Family Medicine, Yongin Severance Hospital, Yonsei University College of Medicine, 363, Dongbaekjukjeon-daero, Giheung-gu, Yongin-si, Gyeonggi-do 16995, Korea. [2]Institute of Advanced Technology, Theragen Health Co. Ltd., Pangyoyeok-ro, Seongnam-si, Gyeonggi-do 13493, Republic of Korea. [3]Department of Family Medicine, Yonsei University College of Medicine, Severance Hospital, Yonsei-ro 50-1, Seodaemun-gu, Seoul 03722, Republic of Korea. [4]Institute for Innovation in Digital Healthcare, Yonsei University, Yonsei-ro 50-1, Seodaemun-gu, Seoul, 03722, Republic of Korea.

References

1. Noubiap JJ, Nansseu JR, Lontchi-Yimagou E, Nkeck JR, Nyaga UF, Ngouo AT, et al. Geographic distribution of metabolic syndrome and its components in the general adult population: a meta-analysis of global data from 28 million individuals. Diabetes Res Clin Pract. 2022;188:109924.
2. Yang YS, Han BD, Han K, Jung JH, Son JW. Obesity fact sheet in Korea, 2021: trends in obesity prevalence and obesity-related comorbidity incidence stratified by age from 2009 to 2019. J Obes Metab Syndr. 2022;31(2):169–77.
3. Dancause KN, Olszowy KM. Identifying actionable lifestyle risk factors for obesity research and intervention: challenges and opportunities

Kwon *et al. Journal of Translational Medicine*   (2024) 22:591

Page 10 of 10

for Pacific Island health researchers. Lancet Reg Health West Pac. 2020;4:100040.

4. Teng ML, Ng CH, Huang DQ, Chan KE, Tan DJ, Lim WH, et al. Global incidence and prevalence of nonalcoholic fatty liver disease. Clin Mol Hepatol. 2023;29(Suppl):S32-s42.

5. Gofton C, Upendran Y, Zheng MH, George J. MAFLD: how is it different from NAFLD? Clin Mol Hepatol. 2023;29(Suppl):S17-s31.

6. Mantovani A, Scorletti E, Mosca A, Alisi A, Byrne CD, Targher G. Complications, morbidity and mortality of nonalcoholic fatty liver disease. Metabolism. 2020;111s:154170.

7. Meroni M, Longo M, Rustichelli A, Dongiovanni P. Nutrition and genetics in NAFLD: the perfect binomium. Int J Mol Sci. 2020. https://doi.org/10.3390/ijms21082986.

8. Trichopoulou A, Martínez-González MA, Tong TY, Forouhi NG, Khandelwal S, Prabhakaran D, et al. Definitions and potential health benefits of the Mediterranean diet: views from experts around the world. BMC Med. 2014;12:112.

9. Mente A, de Koning L, Shannon HS, Anand SS. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. Arch Intern Med. 2009;169(7):659–69.

10. Rossi M, Turati F, Lagiou P, Trichopoulos D, Augustin LS, La Vecchia C, et al. Mediterranean diet and glycaemic load in relation to incidence of type 2 diabetes: results from the Greek cohort of the population-based European prospective investigation into cancer and nutrition (EPIC). Diabetologia. 2013;56(11):2405–13.

11. Estruch R, Ros E, Salas-Salvadó J, Covas MI, Corella D, Arós F, et al. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. N Engl J Med. 2018;378(25):e34.

12. Sofi F, Cesari F, Abbate R, Gensini GF, Casini A. Adherence to Mediterranean diet and health status: meta-analysis. BMJ. 2008;337:a1344.

13. Schwingshackl L, Missbach B, König J, Hoffmann G. Adherence to a Mediterranean diet and risk of diabetes: a systematic review and meta-analysis. Public Health Nutr. 2015;18(7):1292–9.

14. Kwon YJ, Lee H, Yoon Y, Kim HM, Chu SH, Lee JW. Development and validation of a questionnaire to measure adherence to the Mediterranean diet in Korean adults. Nutrients. 2020. https://doi.org/10.3390/nu12041102.

15. Kim Y, Han BG. Cohort profile: the Korean genome and epidemiology study (KoGES) Consortium. Int J Epidemiol. 2017;46(2):e20.

16. Ahn Y, Kwon E, Shim JE, Park MK, Joo Y, Kimm K, et al. Validation and reproducibility of food frequency questionnaire for Korean genome epidemiologic study. Eur J Clin Nutr. 2007;61(12):1435–41.

17. Muniyappa R, Lee S, Chen H, Quon MJ. Current approaches for assessing insulin sensitivity and resistance in vivo: advantages, limitations, and appropriate usage. Am J Physiol Endocrinol Metab. 2008;294(1):E15-26.

18. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension: the task force for the management of arterial hypertension of the European society of cardiology and the European society of hypertension: the task force for the management of arterial hypertension of the European society of cardiology and the European society of hypertension. J Hypertens. 2018;36(10):1953–2041.

19. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2020. Diabetes Care. 2020;43(Suppl 1):S14-s31

20. Kim KK, Haam JH, Kim BT, Kim EM, Park JH, Rhee SY, et al. Evaluation and treatment of obesity and its comorbidities: 2022 update of clinical practice guidelines for obesity by the Korean society for the study of obesity. J Obes Metab Syndr. 2023;32(1):1–24.

21. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: an international expert consensus statement. J Hepatol. 2020;73(1):202–9.

22. Lee H, Lee HW, Kim SU, Chang KH. Metabolic dysfunction-associated fatty liver disease increases colon cancer risk: a nationwide cohort study. Clin Transl Gastroenterol. 2022;13(1):e00435.

23. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. Diabetologia. 2016;59(6):1121–40.

24. Moon S, Kim YJ, Han S, Hwang MY, Shin DM, Park MY, et al. The Korea biobank array: design and identification of coding variants associated with blood biochemical traits. Sci Rep. 2019;9(1):1382.

25. Qi Q, Wu Y, Li H, Loos RJ, Hu FB, Sun L, et al. Association of GCKR rs780094, alone or in combination with GCK rs1799884, with type 2 diabetes and related traits in a Han Chinese population. Diabetologia. 2009;52(5):834–43.

26. Zahedi AS, Akbarzadeh M, Sedaghati-Khayat B, Seyedhamzehzadeh A, Daneshpour MS. Correction: GCKR common functional polymorphisms are associated with metabolic syndrome and its components: a 10-year retrospective cohort study in Iranian adults. Diabetol Metab Syndr. 2023;15(1):99.

27. Bi M, Kao WH, Boerwinkle E, Hoogeveen RC, Rasmussen-Torvik LJ, Astor BC, et al. Association of rs780094 in GCKR with metabolic traits and incident diabetes and cardiovascular disease: the ARIC Study. PLoS ONE. 2010;5(7):e11690.

28. Mohammadi S, Farajnia S, Shadmand M, Mohseni F, Baghban R. Association of rs780094 polymorphism of glucokinase regulatory protein with non-alcoholic fatty liver disease. BMC Res Notes. 2020;13(1):26.

29. Lin YC, Chang PF, Chang MH, Ni YH. Genetic variants in GCKR and PNPLA3 confer susceptibility to nonalcoholic fatty liver disease in obese individuals. Am J Clin Nutr. 2014;99(4):869–74.

30. Ford BE, Chachra SS, Rodgers K, Moonira T, Al-Oanzi ZH, Anstee QM, et al. The GCKR-P446L gene variant predisposes to raised blood cholesterol and lower blood glucose in the P446L mouse-a model for GCKR rs1260326. Mol Metab. 2023;72:101722.

31. Fernandes Silva L, Vangipurapu J, Kuulasmaa T, Laakso M. An intronic variant in the GCKR gene is associated with multiple lipids. Sci Rep. 2019;9(1):10240.

32. Ashcroft FM, Lloyd M, Haythorne EA. Glucokinase activity in diabetes: too much of a good thing? Trends Endocrinol Metab. 2023;34(2):119–30.

33. Zhang Z, Ji G, Li M. Glucokinase regulatory protein: a balancing act between glucose and lipid metabolism in NAFLD. Front Endocrinol. 2023;14:1247611.

34. Park JM, Kim TH, Jo SH, Kim MY, Ahn YH. Acetylation of glucokinase regulatory protein decreases glucose metabolism by suppressing glucokinase activity. Sci Rep. 2015;5:17395.

35. Orho-Melander M, Melander O, Guiducci C, Perez-Martinez P, Corella D, Roos C, et al. Common missense variant in the glucokinase regulatory protein gene is associated with increased plasma triglyceride and C-reactive protein but lower fasting glucose concentrations. Diabetes. 2008;57(11):3112–21.

36. Saxena R, Voight BF, Lyssenko V, Burtt NP, de Bakker PI, Chen H, et al. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. Science. 2007;316(5829):1331–6.

37. Nettleton JA, McKeown NM, Kanoni S, Lemaitre RN, Hivert MF, Ngwa J, et al. Interactions of dietary whole-grain intake with fasting glucose- and insulin-related genetic loci in individuals of European descent: a meta-analysis of 14 cohort studies. Diabetes Care. 2010;33(12):2684–91.

38. Perez-Martinez P, Delgado-Lista J, Garcia-Rios A, Mc Monagle J, Gulseth HL, Ordovas JM, et al. Glucokinase regulatory protein genetic variant interacts with omega-3 PUFA to influence insulin resistance and inflammation in metabolic syndrome. PLoS ONE. 2011;6(6):e20555.

39. Slosberg ED, Desai UJ, Fanelli B, St Denny I, Connelly S, Kaleko M, et al. Treatment of type 2 diabetes by adenoviral-mediated overexpression of the glucokinase regulatory protein. Diabetes. 2001;50(8):1813–20.

40. Pollin TI, Jablonski KA, McAteer JB, Saxena R, Kathiresan S, Kahn SE, et al. Triglyceride response to an intensive lifestyle intervention is enhanced in carriers of the GCKR Pro446Leu polymorphism. J Clin Endocrinol Metab. 2011;96(7):E1142–7.

41. Machado MV, Cortez-Pinto H. Non-invasive diagnosis of non-alcoholic fatty liver disease. A critical appraisal J Hepatol. 2013;58(5):1007–19.

42. Kim JH, Kwon SY, Lee SW, Lee CH. Validation of fatty liver index and lipid accumulation product for predicting fatty liver in Korean population. Liver Int. 2011;31(10):1600–1.

Publisher's Note