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Association of *FHIT* gene variant and salty food preference with the incidence of metabolic syndrome

Jihyun Kim[1†], Suyeon Lee[1†], Shiva Raj Acharya[2] and Dayeon Shin[1*]

Abstract

Background Taste perception plays a critical role in determining dietary choices and adherence to specific dietary patterns, which may lead to metabolic syndrome (MetS). The fragile histidine triad diadenosine triphosphatase (*FHIT*) gene plays a key role in cellular processes such as apoptosis and DNA repair, and thus may be an important factor in metabolic regulation. Despite this, the relationship between preference for salty foods, *FHIT* variants, and MetS is still largely unexplored. This study aimed to investigate the interaction between salty food preference and *FHIT* variation on the risk of MetS in middle-aged Korean adults.

Results Over a mean follow-up of 10.6 years, 796 MetS cases were recorded. With regard to MetS incidence, the interaction between the *FHIT* rs2006807 variant and salty food preference was shown in women. Notably, women with the CA/CC genotype who preferred salty foods had a 1.42-fold higher incidence of MetS compared to those with the AA genotype who disliked salty foods (hazard ratio 1.42, 95% confidence interval 1.03–1.97).

Conclusions This study highlights the potential impact of genetic factors and taste preferences when combined on the risk of MetS. Specifically, our findings suggest a significant genetic association between the *FHIT* rs2006807 variant and preference for salty foods, indicating that genetic predisposition may influence dietary choices. These results imply that personalized nutritional strategies that consider both genetic variations and individual dietary preferences may be effective in preventing MetS.

Keywords Metabolic syndrome, *FHIT* gene variants, Salty foods, Korean adults

Introduction

Metabolic syndrome (MetS) is characterized by a set of conditions, including obesity, dyslipidemia, hyperglycemia, and hypertension, that increase the risk of type 2 diabetes, cardiovascular disease (CVD), and mortality rates [1, 2]. Over the past several decades, the global prevalence of MetS has significantly increased, impacting both clinical care and public health [3]. Estimates show that the worldwide prevalence of MetS among adults ranged from 12.5 to 31.4% in 2021 [4]. In most countries across the Americas (USA: 41.8% in 2018, Mexico: 49.8% in 2022), Europe and the Mediterranean (Portugal: 43.1%

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in 2009, Turkey: 34.6% in 2010, Croatia: 44% in 2020), Sub-Saharan Africa (Ghana: 41% in 2020, Nigeria: 23% in 2020), and the Asia-Pacific regions (Japan: 28.5% in 2023, China: 24.5% in 2018), studies report that 15–50% of the adult population is affected by MetS [2, 5–11]. In Korea, the prevalence of MetS has notably increased since 2001, ranging from 27.1 to 33.2%. Among Korean adults, 27.7% of those aged ≤ 30 years and 50% of those aged ≥ 65 years have MetS, with an increasing trend observed among men in their 30s and 40s and women over 70 years according to data published in 2021 [2, 3, 12]. As MetS-associated diseases persist longer in the population, disability-adjusted life years (DALYs) and the economic burden linked to MetS and related diseases are anticipated to increase markedly [2, 4]. Thus, it is critical to systematically explore and address potential risk factors to reduce and prevent the prevalence of MetS.

MetS is primarily the result of overnutrition, poor dietary choices, and a sedentary lifestyle, leading to adiposity and subsequent metabolic issues [1, 7]. Among the multifaceted factors which influence MetS, taste perception significantly determines dietary choices and thereby affects the risk of obesity and diabetes [13–15]. Previous studies have identified the overconsumption of salty foods as a key factor that induces metabolic disorders, including hypertension, insulin resistance, and endothelial dysfunction in both human and animal models [5, 16, 17]. Moreover, obese individuals prefer salty foods and exhibit decreased salt sensitivity [5, 18]. However, findings on the impact of a preference for salty foods on MetS and its related diseases are varied and unclear [17, 19–23]. Some studies suggest that greater salt taste sensitivity and preference are linked to lower odds of MetS [5, 19, 24]. Conversely, other studies indicate that a preference for salty foods is associated with higher risks of these conditions, highlighting the intricate nature of this relationship [22, 23, 25]. In contrast, a notable positive link was observed between preferences for sweet, spicy, and sour tastes, and obesity and body composition, especially in middle-aged and older adults [14, 20, 23]. Moreover, older adults with a liking for sweet and spicy foods have been found to have an increased risk of cardiometabolic diseases, whereas a preference for salt seems to indicate lower risk, suggesting a complex interplay between age, taste preferences, and disease risk [20, 26, 27]. Nevertheless, studies on the relationship between a preference for salty foods and MetS are limited and this relationship has not been comprehensively investigated [5, 23]. This gap in research underscores the need for more detailed studies to explore how these preferences develop over time and their long-term impact on health.

Genomic variants have pinpointed several susceptibility factors associated with the traits of MetS [13, 28]. Among the numerous variants identified by genome-wide association studies (GWAS) that have offered insights into the pathogenesis of MetS, the fragile histidine triad diadenosine triphosphatase (*FHIT*) gene has emerged as a significant variant [28, 29]. The *FHIT* gene plays a critical role in cellular processes such as apoptosis and DNA repair, making it a crucial factor in metabolic regulation [29, 30]. While primarily recognized as a tumor suppressor gene [30], there is growing interest in understanding how its variants might contribute to the risk of MetS. Some studies have suggested a positive association between *FHIT* gene variants and obesity, with certain single nucleotide polymorphisms (SNPs) contributing to an increase of approximately 0.1 units in body mass index (BMI) or 0.3 kg of weight in tall individuals [28, 31]. In addition, *FHIT* is also implicated in metabolic processes, including those associated with MetS components such as blood pressure and diabetes [32, 33]. However, the exact mechanisms and the strength of this association remain underexplored and require further investigation [28]. Given the various taste preferences found to be associated with MetS and its components [23, 25, 26], it is essential to assess how genetic variations and specific genotypes might interact with preference for salty taste to influence the progression of MetS. Since MetS significantly increases the risk of type 2 diabetes, CVD, and cancer [1, 3, 5], any additional insights on the contributing factors and interrelationships could help in the development of targeted interventions. Recent GWAS have identified the *FHIT* gene as a potential contributor to MetS. While genetic factors play a crucial role in MetS development, dietary preferences, particularly salt intake, may interact with genetic variants to influence disease risk. However, the interaction between the *FHIT* gene variants and salty food preference in relation to MetS remains largely unexplored. Therefore, this study aimed to investigate how the *FHIT* rs2006807 variant and salty food preference interact to affect MetS incidence in middle-aged and older Korean adults. Thus, this study aimed to investigate the effects of the *FHIT* rs2006807 variant and a preference for salty foods on the incidence of MetS in middle-aged and older Korean adults.

Methods

Study settings and participants

We utilized data from the Ansan-Ansung cohort of the Korean Genome and Epidemiology Study (KoGES). The KoGES Ansan-Ansung study included 10,030 participants aged 40–69 years. The baseline recruitment of the study was conducted between 2001 and 2002, with participants followed up every two years. The data used in this study spans from the baseline (2001–2002) to the seventh follow-up examination (2015–2016). Details on KoGES have been described elsewhere [34]. Participants with no data on the *FHIT* rs2006807 genotypes ($n = 1,221$),

salty food preferences ($n = 107$), MetS ($n = 5{,}558$), MetS at baseline ($n = 812$), and potential confounders ($n = 520$) were excluded from the study. Therefore, the analysis as presented in Fig. 1 included 1,812 (885 men and 927 women) final study participants. The study adhered to the principles outlined in the Declaration of Helsinki and received approval from the Institutional Review Board of Inha University (IRB No. 240307–1 A). Written informed consent was obtained from all participants.

Assessment of preference for salty foods

In the KoGES, information about participants' dietary information and food preferences was assessed using a validated questionnaire administered by well-trained interviewers [35, 36]. The participants rated their preference for salty foods on a five-point scale, ranging from "very much like" to "very much dislike". In this study, participants were further categorized into two groups based on their level of preference: those with an average to a strong preference for salty foods ("average," "like," and "very much like") were classified as "like," whereas those who did not prefer salty foods ("dislike" and "very much dislike") were classified as "dislike".

Assessment of MetS

MetS was assessed based on the criteria recommended by the National Cholesterol Education Program-Adult Treatment Panel (NCEP-ATP III) [37]. MetS is considered present if three or more of the following five criteria are met: [1] abdominal obesity (waist circumference ≥ 80 cm in women and ≥ 90 cm in men); [2] hyperglycemia (fasting blood sugar ≥ 110 mg/dL, diagnosed with diabetes or currently on diabetes medication; [3] hypertriglyceridemia (plasma triglyceride concentration ≥ 150 mg/dL); [4] low high-density lipoprotein cholesterol (HDL-C, plasma HDL-C concentration < 50 mg/

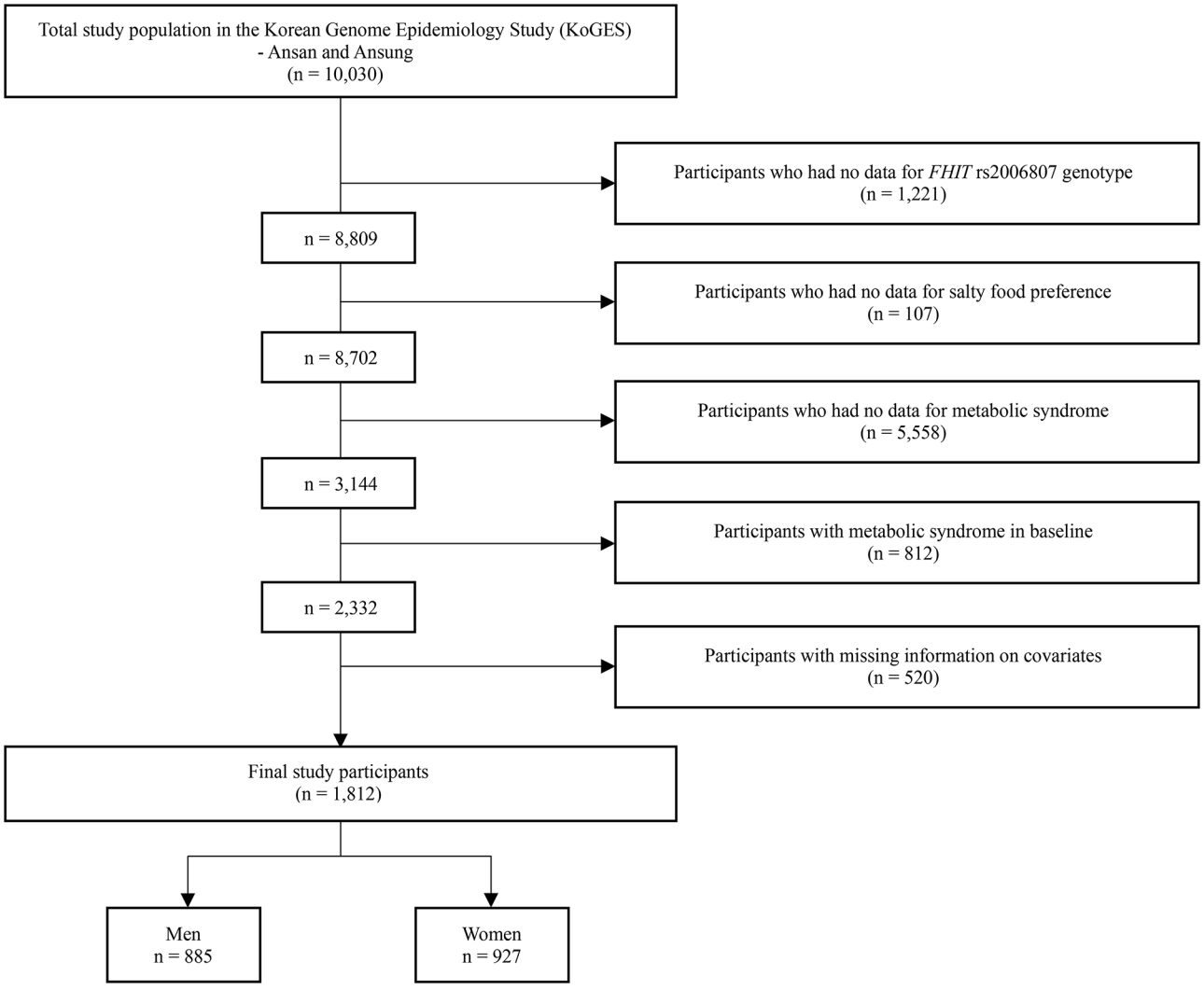

Fig. 1 Flow diagram of the study design, including the study participants inclusion and elimination criteria

dL in women; < 40 mg/dL in men; [5] elevated blood pressure (systolic blood pressure [SBP] ≥ 130 mmHg, diastolic blood pressure [DBP] ≥ 85mmHg, diagnosed with hypertension, or currently on antihypertensive medication) [38–40].

Genotyping and imputation

Korean genomic data were genotyped using the Affymetrix Genome-Wide Human SNP Array 5.0 (Affymetrix, Santa Clara, CA, USA). After genotyping, GWAS was performed on the entire sample to identify SNPs associated with participants' preference for salty foods, adjusting for sex and age. To ensure the quality of the data, SNP markers that deviated from Hardy-Weinberg equilibrium with a p-value $< 1 \times 10^{-6}$ were excluded from the analysis, as Hardy-Weinberg equilibrium is an important indicator of genotyping quality and population structure [41]. The *FHIT* rs2006807, with a p-value of 2.02×10^{-5} was selected, as illustrated in Fig. 2. *FHIT* rs2006807 is located on chromosome 3, and the SNP is situated within an intron 5 of *FHIT*. Using regional plots, we identified 341 SNPs between 59705075 bp and 61217173 bp on chromosome 3 (Fig. 3). The *FHIT* rs2006807 is most statistically significant on chromosome 3, and shows a high r^2 value with surrounding SNPs in the plot, indicating a strong genetic relationship. In this study, 8,809 SNPs corresponding to *FHIT* rs2006807 were analyzed. Furthermore, the CC genotype of rs2006807 was classified as the major genotype, while the CA and AA genotypes were categorized as minor genotypes.

The SNPs shown in the figure are located on chromosome 3: 59.7–61.2 Mb, with the highlighted rs2006807 representing a key SNP. The SNPs are plotted by their statistical significance (-log10 p-value), the purple diamond (rs2006807) is the most significantly associated with preference for salty foods in Korean adults.

Statistical analyses

GWAS analysis to select SNPs associated with salty food preference was performed using PLINK software (version 1.9, https://www.cog-genomics.org/plink/1.9) [42]. SNPs and genotype frequencies associated with the preference for salty foods were identified with logistic regression analysis. Three different genetic models (CA, CC, AA) were selected and further categorized into two models (CA, CC vs. AA) for the analysis. The data used for expression quantitative trait loci (eQTL) analysis were obtained via the GTEx browser (https://gtexportal.org/). Haploview was used for Manhattan plots and linkage disequilibrium (LD) block. To obtain regional association plots, the web-based program Locuszoom version 1.3 (http://csg.sph.umich.edu/locuszoom/) was used.

The baseline characteristics are presented using descriptive statistics and include frequencies, percentages, and means ± standard deviations (SDs). Differences between the groups categorized according to the MetS status and genotype were assessed using t-tests and generalized linear models for continuous variables, and Chi-square tests for categorical variables. Additionally, a multivariable Cox proportional hazards model was employed to calculate the adjusted hazard ratios (HRs) for the incidence of MetS based on the genotype and preference for salty foods. In the analysis, we incorporated several demographic and lifestyle factors as

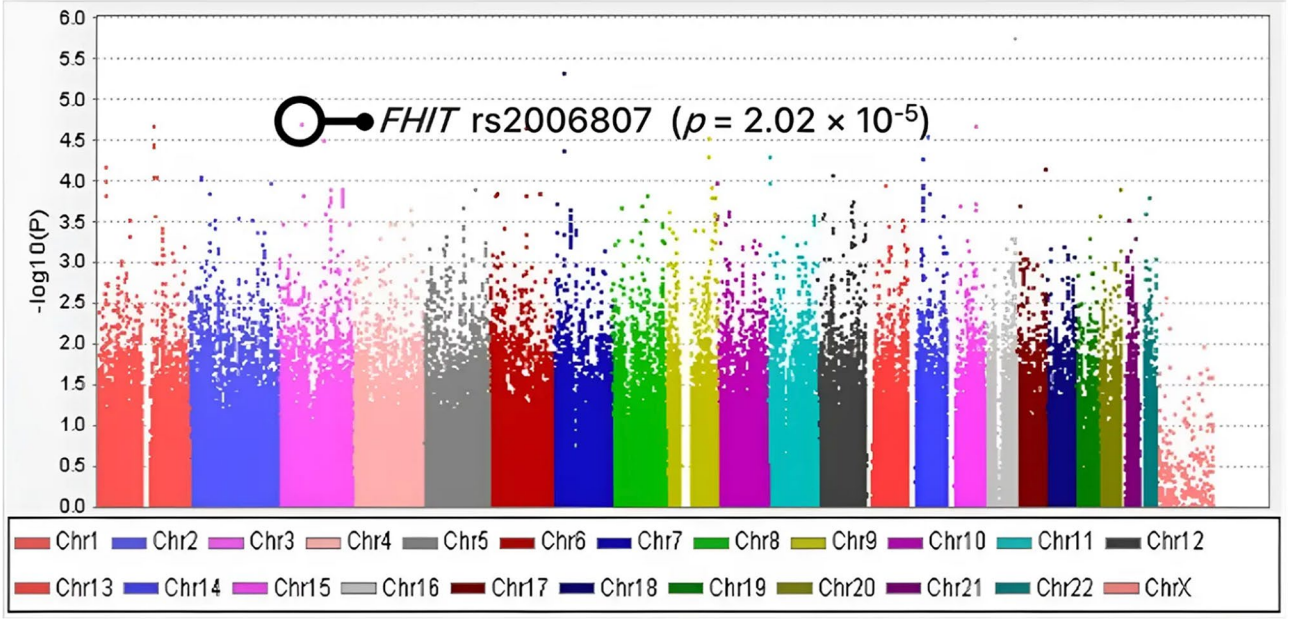

Fig. 2 Manhattan plots for the genome-wide association study (GWAS) of salty food preference

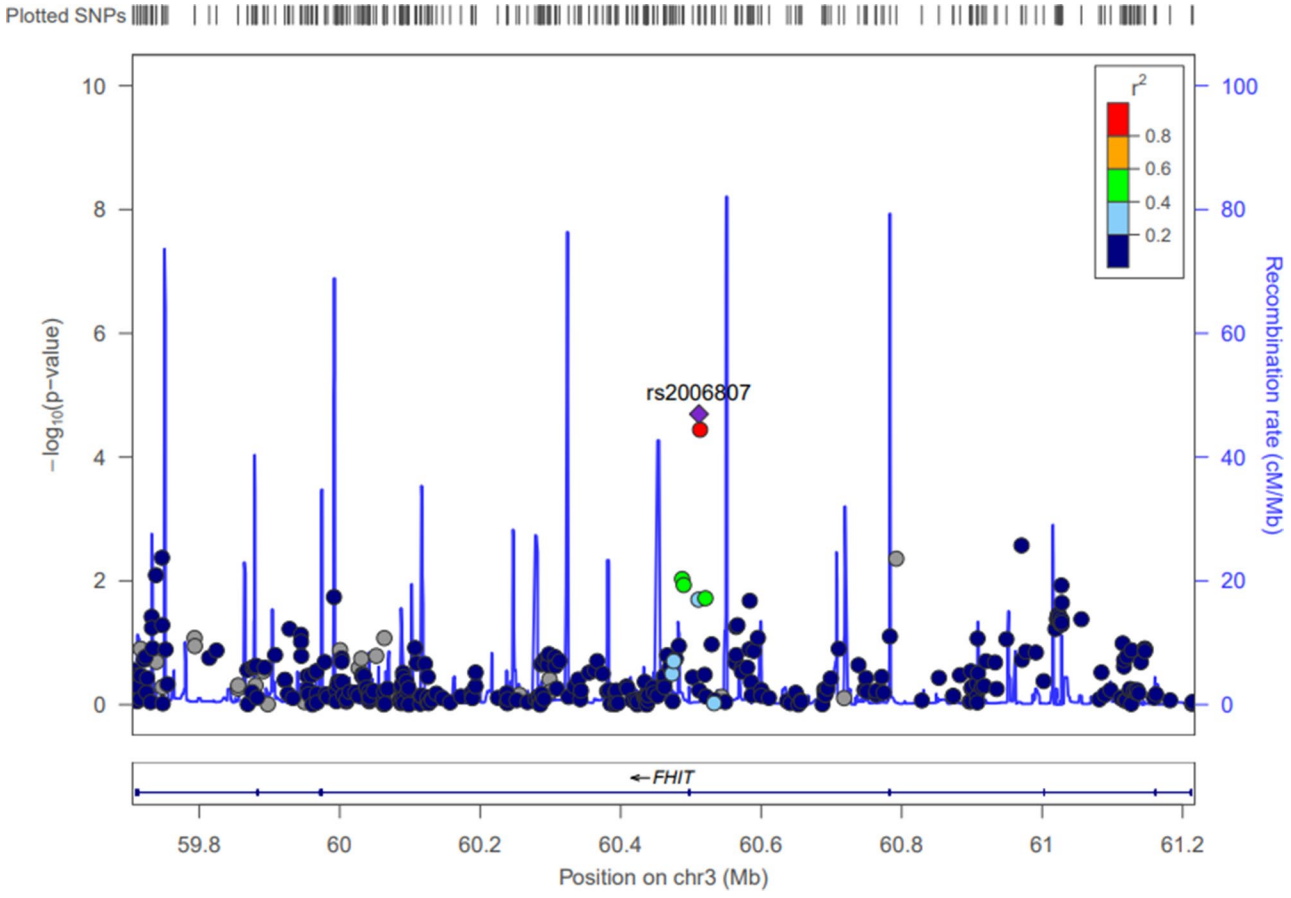

Fig. 3 Regional plot for single nucleotide polymorphisms (SNPs) on *FHIT* gene that are significantly associated with preference for salty foods

potential confounders. These include age (years), income (< 1 million won/month, 1–3 million won/month, ≥ 3 million won/month), education level (elementary or technical college/university/graduate school), residency area (Ansan, Ansung), smoking status (never, past, current), alcohol intake (never, past, current), BMI (kg/m^2), physical activity (metabolic equivalent of task, MET-hours/week), and energy intake (kcal/day). In Model 1, age was adjusted, and in Model 2, age, area, BMI, smoking status, drinking status, education, income, total energy intake, and MET were adjusted. Baseline characteristic comparisons and multivariable Cox proportional hazards models were performed stratified by sex, and significance was considered to be $p < 0.05$. These data were analyzed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

General characteristics of the study participants based on the presence of MetS

The baseline characteristics of the participants according to the incidence of MetS are depicted in Table 1. The average follow-up period was 10.6 years, and 796 cases of MetS were recorded. The participants were divided into groups with MetS ($n = 796$) and without MetS ($n = 1,016$) at the end of the follow-up. There was a significant difference in the preference for salty foods between both men and women. In both groups with and without MetS, the proportion of participants who preferred salty foods was higher than the proportion who did not ($p < 0.05$). Women with MetS were older than women without MetS ($p < 0.05$). MetS components such as BMI, waist circumference, systolic and diastolic blood pressure, triglyceride levels, and fasting blood glucose levels were significantly higher in the group with MetS than in the group without MetS in both men and women, whereas HDL-cholesterol levels were significantly lower ($p < 0.05$). Total energy and carbohydrate intakes were higher in women with MetS than in women without MetS ($p < 0.05$). In both men and women, the rate of Ansan (urban) was higher than that of Ansung (rural) in both groups, with and without MetS ($p < 0.05$). Significant differences in education and income levels were identified only among women. In terms of education level, both groups with and without MetS had the highest elementary/technical college graduation rates. Regarding the income level, both groups with and without MetS showed the highest rate of spending 1 to 3 million won per month. There was a significant difference in smoking status among men, with the group with

Table 1 General characteristics of the study participants based on the presence of metabolic syndrome

Variables	Men			Women		
	Metabolic syndrome (*n* = 404)	No metabolic syndrome (*n* = 481)	*p*-value	Metabolic syndrome (*n* = 392)	No metabolic syndrome (*n* = 535)	*p*-value
***FHIT* rs2006807**						
AA	224 (25.31%)	252 (28.47%)	0.3639	201 (21.68%)	302 (32.58%)	0.1183
CC/CA	180 (20.34%)	229 (25.88%)		191 (20.60%)	233 (25.13%)	
Salty food preference						
Dislike	128 (14.46%)	191 (21.58%)	0.0133	130 (14.02%)	230 (24.81%)	0.0024
Like	276 (31.19%)	290 (32.77%)		262 (28.26%)	305 (32.90%)	
Age (years)	49.36 ± 7.32	49.40 ± 7.68	0.9341	51.21 ± 8.09	47.30 ± 6.69	< 0.0001
BMI (kg/m^2)	24.81 ± 2.42	23.13 ± 2.39	< 0.0001	25.04 ± 2.77	23.36 ± 2.45	< 0.0001
Waist circumference (cm)	84.39 ± 5.80	79.37 ± 6.10	< 0.0001	80.93 ± 7.34	74.85 ± 7.17	< 0.0001
Systolic blood pressure (mmHg)	119.63 ± 15.23	114.00 ± 13.51	< 0.0001	118.27 ± 15.22	107.33 ± 13.66	< 0.0001
Diastolic blood pressure (mmHg)	81.24 ± 10.29	77.04 ± 9.51	< 0.0001	77.51 ± 9.22	71.09 ± 8.80	< 0.0001
Triglycerides (mg/dL)	176.42 ± 101.80	127.60 ± 55.27	< 0.0001	128.22 ± 67.96	108.38 ± 49.80	< 0.0001
Glucose (mg/dL)	86.38 ± 8.75	83.74 ± 8.78	< 0.0001	81.90 ± 8.12	79.47 ± 6.63	< 0.0001
HDL-cholesterol (mg/dL)	41.75 ± 7.85	47.38 ± 10.08	< 0.0001	46.29 ± 9.60	50.03 ± 9.91	< 0.0001
Nutritional intake						
Total calories (kcal/day)	2027.76 ± 557.99	1986.41 ± 509.30	0.2498	1914.55 ± 641.23	1825.99 ± 537.78	0.0266
Protein (g/day)	70.28 ± 23.31	68.05 ± 22.11	0.1447	64.65 ± 26.00	63.14 ± 22.46	0.3580
Fat (g/day)	36.83 ± 17.43	35.97 ± 16.68	0.4549	29.85 ± 16.44	31.05 ± 15.34	0.2549
Carbohydrate (g/day)	348.22 ± 94.97	342.22 ± 83.96	0.3238	342.19 ± 114.23	319.17 ± 92.96	< 0.0011
Area						
Ansung	126 (14.24%)	104 (11.75%)	0.0012	182 (19.63%)	95 (10.25%)	< 0.0001
Ansan	278 (31.41%)	377 (42.60%)		210 (22.65%)	440 (47.46%)	
Education						
Elementary/technical college	329 (37.18%)	383 (43.28%)	0.5326	375 (40.45%)	487 (52.54%)	0.0154
University	63 (7.12%)	77 (8.70%)		14 (1.51%)	44 (4.75%)	
Graduate school	12 (1.36%)	21 (2.37%)		3 (0.32%)	4 (0.43%)	
Income (million won/month)						
< 1	73 (8.25%)	82 (9.27%)	0.5709	128 (13.81%)	93 (10.03%)	< 0.0001
1–3	210 (23.73%)	267 (30.17%)		197 (21.25%)	321 (34.63%)	
≥ 3	121 (13.67%)	132 (14.92%)		67 (7.23%)	121 (13.05%)	
Smoking						
Never	79 (8.93%)	128 (14.46%)	0.0002	379 (40.88%)	525 (56.63%)	0.3753
Past	123 (13.90%)	179 (20.23%)		4 (0.43%)	3 (0.32%)	
Current	202 (22.82%)	174 (19.66%)		9 (0.97%)	7 (0.76%)	
Drinking						
Never	71 (8.02%)	88 (9.94%)	0.2205	238 (27.83%)	368 (39.70%)	0.1664
Past	22 (2.49%)	40 (4.52%)		15 (1.62%)	10 (1.08%)	
Current	311 (35.14)	353 (39.89%)		119 (12.84%)	157 (16.94%)	
Physical activity						
MET (hours/week)	165.92 ± 100.72	153.50 ± 91.09	0.0568	167.56 ± 103.10	143.67 ± 82.82	0.0002

Categorical and continuous variables are presented as frequencies (%) and mean ± SD, respectively

FHIT, fragile histidine triad diadenosine triphosphatase; BMI, body mass index; HDL, high-density lipoprotein; MET, metabolic equivalent of task

MetS having the highest percentage of current smokers, and the group without MetS having the highest percentage of former smokers. There was a significant difference in physical activity level only in women, and women with MetS had higher MET levels than women without MetS.

General characteristics of the study participants based on *FHIT* variant genotypes

Table 2 shows the baseline characteristics of the study participants according to the genotypes (AA, CC, and CA) of the *FHIT* rs2006807 variant. In women, the rs2006807 AA and CC/CA genotypes had a higher proportion of those who preferred salty foods than those who did not. Only in men, there were significant

Table 2 General characteristics of the study participants based on the *FHIT* rs2006807 genotypes

Variables	Men			Women		
	AA (*n* = 476)	CC/CA (*n* = 409)	*p*-value	AA (*n* = 503)	CC/CA (*n* = 424)	*p*-value
Salty food preference						
Dislike	169 (19.10%)	150 (16.95%)	0.7176	171 (18.45%)	189 (20.39%)	0.0010
Like	307 (34.69%)	259 (29.27%)		332 (35.81%)	235 (25.35%)	
Age (years)	49.63 ± 7.60	49.09 ± 7.40	0.2852	49.06 ± 7.65	48.83 ± 7.47	0.6462
BMI (kg/m^2)	23.99 ± 2.51	23.80 ± 2.58	0.2516	24.00 ± 2.82	24.15 ± 2.60	0.4130
Waist circumference (cm)	81.86 ± 6.26	81.43 ± 6.70	0.3348	77.45 ± 7.93	77.39 ± 7.74	0.9157
Systolic blood pressure (mmHg)	116.95 ± 14.93	116.13 ± 14.18	0.4099	111.28 ± 14.96	112.77 ± 15.71	0.1406
Diastolic blood pressure (mmHg)	79.33 ± 10.17	78.51 ± 9.98	0.2262	73.49 ± 9.18	74.18 ± 9.91	0.2716
Triglycerides (mg/dL)	150.13 ± 89.83	149.60 ± 75.60	0.9239	119.33 ± 66.94	113.74 ± 47.71	0.1397
Glucose (mg/dL)	84.70 ± 8.82	85.23 ± 8.91	0.3713	80.29 ± 7.36	80.73 ± 7.43	0.3677
HDL-cholesterol (mg/dL)	44.48 ± 8.92	45.19 ± 10.22	0.2723	48.49 ± 10.04	48.40 ± 9.85	0.8904
Nutritional intake						
Total calories (kcal/day)	1999.63 ± 532.54	2011.87 ± 532.32	0.7332	1850.33 ± 572.10	1878.99 ± 600.41	0.4577
Protein (g/day)	68.46 ± 22.49	69.78 ± 22.91	0.3885	63.58 ± 24.85	64.01 ± 23.03	0.7853
Fat (g/day)	35.32 ± 16.91	37.58 ± 17.10	0.0492	30.17 ± 16.38	30.98 ± 15.14	0.4406
Carbohydrate (g/day)	346.62 ± 91.08	343.03 ± 86.93	0.5500	326.65 ± 97.88	331.58 ± 108.9	0.4724
Area						
Ansung	129 (14.58%)	101 (11.41%)	0.4157	155 (16.72%)	122 (13.16%)	0.4987
Ansan	347 (39.21%)	308 (34.80%)		348 (37.54%)	302 (32.58%)	
Education						
Elementary/technical college	380 (42.94%)	332 (37.51%)	0.5117	472 (50.92%)	390 (42.07%)	0.2236
University	75 (8.47%)	65 (7.34%)		26 (2.80%)	32 (3.45%)	
Graduate school	21 (2.37%)	12 (1.36%)		5 (0.54%)	2 (0.22%)	
Income (million won/month)						
< 1	81 (9.15%)	74 (8.36%)	0.1636	119 (12.85%)	102 (11.00%)	0.8481
1–3	270 (30.51%)	207 (23.39%)		285 (30.74%)	233 (25.13%)	
≥ 3	125 (14.12%)	128 (14.46%)		99 (10.68%)	89 (9.60%)	
Smoking						
Never	107 (12.09%)	100 (11.30%)	0.4845	490 (52.86%)	414 (44.66%)	0.6220
Past	158 (17.85%)	144 (116.27%)		5 (0.54%)	2 (0.22%)	
Current	211 (23.84%)	165 (18.64%)		8 (0.86%)	8 (0.86%)	
Drinking						
Never	88 (9.94%)	71 (8.02%)	0.8688	345 (37.22%)	281 (30.31%)	0.2015
Past	32 (3.62%)	30 (3.39%)		17 (1.83%)	8 (8.86%)	
Current	356 (40.23%)	308 (34.80%)		141 (15.21%)	135 (14.56%)	
Physical activity						
MET (hours/week)	152.20 ± 93.62	167.28 ± 97.67	0.0198	151.68 ± 91.75	156.25 ± 93.75	0.4556

Categorical and continuous variables are presented as frequencies (%) and mean ± SD, respectively

FHIT, fragile histidine triad diadenosine triphosphatase; BMI, body mass index; HDL, high-density lipoprotein; MET, metabolic equivalent of task

differences in physical activity levels between thee CC/CA and AA genotypes, with men in the CC/CA genotype having higher MET values compared to the AA genotype. Other variables did not differ significantly between groups.

Functional annotations of *FHIT* variants with eQTL

This study performed eQTL analysis based on the GTEx database to determine gene expression levels according to SNP genotypes. eQTLs were uncovered for the SNP (rs2006807) in human tissues. As a result, the AA genotype of rs2006807 contributed to lower expression levels of the *FHIT* gene in the adrenal gland, while the CC genotype contributed to higher expression levels of the *FHIT* gene in the adrenal gland ($p = 1.05 \times 10^{-6}$) (Fig. 4). These results demonstrate that the expression of the *FHIT* gene in human tissue differs depending on the genotypes of the *FHIT* gene.

The expression of genotype rs2006807 in the chr3_60550687_A_C_b38 region. The gene expression of each genotype in the adrenal gland was presented using GTEx Portal and showed statistical significance

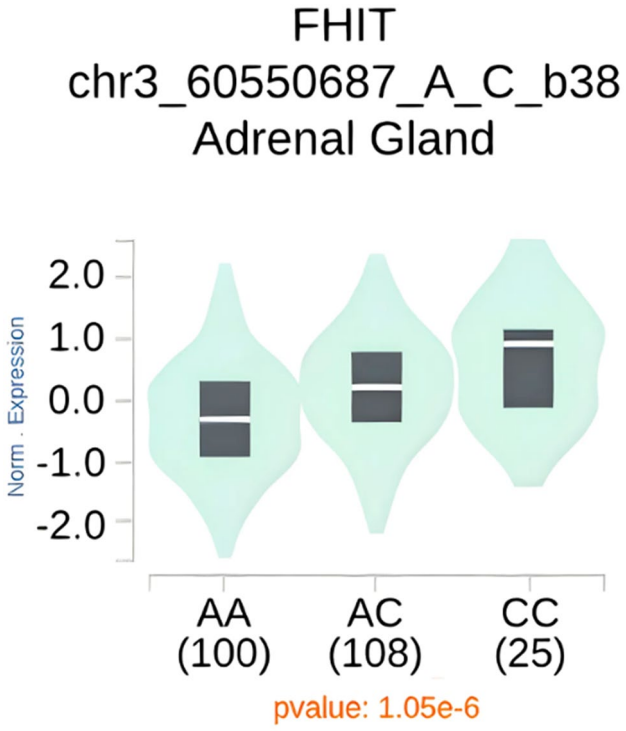

Fig. 4 Identification of the gene expression of the *FHIT* gene and SNPs in eQTL

($p = 1.05 \times 10^{-6}$). The white line indicates mean expression levels, and the black box indicate 25% and 75% quantiles. Data were obtained via the GTEx browser (https://gtexportal.org/).

LD block structure of SNPs in the *FHIT* gene

The LD blocks were analyzed for SNPs associated with the *FHIT* gene using the Haploview program based on Korean genomic data. The SNPs rs2006807, rs107342, and rs6762597 are associated with each other, indicating a potential linkage among these variants within the *FHIT* gene region (Fig. 5).

It includes the SNP (rs2006807) located within the *FHIT* gene, with the LD block visually represented below. The colors indicate the strength of LD between different SNPs, with red representing stronger LD. The numbers in each cell indicate that a higher value signifies a stronger association between the two SNPs. This plot was generated using Haploview software.

Association between preference for salty foods and MetS

Table 3 shows the incidence of MetS according to a preference for salty foods. A significant positive association between salty food preference and MetS was observed in both the unadjusted model for men and women and in Model 1 adjusted for age ($P < 0.05$). However, the significant association disappeared in Model 2, which adjusted for all demographic and health-related variables.

Association between the *FHIT* rs2006807 genotype and MetS

Table 4 shows the incidence of MetS according to the *FHIT* rs2006807 genotype. In all models, there was no statistically significant difference in the incidence of MetS based on salty food preferences in both men and women.

Incidence of MetS according to preference for salty foods and the *FHIT* rs2006807 genotype

Table 5 shows the incidence of MetS according to the combination of preference for salty foods and the *FHIT* rs2006807 genotype. In all models, regardless of covariate adjustment, women showed significant differences in the incidence of MetS according to salty food preference and genetic variation. In model 2, which adjusted for both demographic and health-related variables, the incidence of MetS was 1.42 times higher in women with the CC/CA genotype who preferred salty foods than in women with the AA genotype who did not prefer salty foods (HR 1.42, 95% CI 1.03–1.97).

Supplementary Table 1 shows the incidence of MetS according to the combination of salty food preference and *FHIT* rs2006807 genotype in the entire population, regardless of gender. The incidence of MetS in the entire population showed significant differences according to salty food preference and genetic variation. The incidence of MetS was 1.22 times higher in the CC/CA genotype, which prefers salty food, than in the AA genotype, which does not prefer salty food (HR 1.22, 95% CI 0.98–1.51).

Discussion

In this prospective cohort study, we explored the impact of the *FHIT* rs2006807 gene variant and a preference for salty food on the incidence of MetS among middle-aged and older adults in Korea. *FHIT* rs2006807 and preference for salty food were not significantly associated with MetS, but these two variables interacted to have a significant effect. Specifically, women with the CC/CA genotype of *FHIT* rs2006807 and a preference for salty foods had the highest risk of MetS compared to those with the AA genotype who disliked salty food. These findings highlight the significant interplay between genetic variants, taste preference, and MetS, and underscore the importance of considering gender differences in future research and interventions related to MetS.

In this study, a preference for salty foods alone was not significantly associated with MetS. Previous studies have investigated the association between salt intake and MetS, and have emphasized the detrimental effects of consuming salt-rich foods on MetS [5, 20, 24, 25]. However, the association between MetS and taste perception or dietary choices, such as a preference for salty foods, has not been extensively studied. A cross-sectional study conducted in Croatia showed that the lower the salt

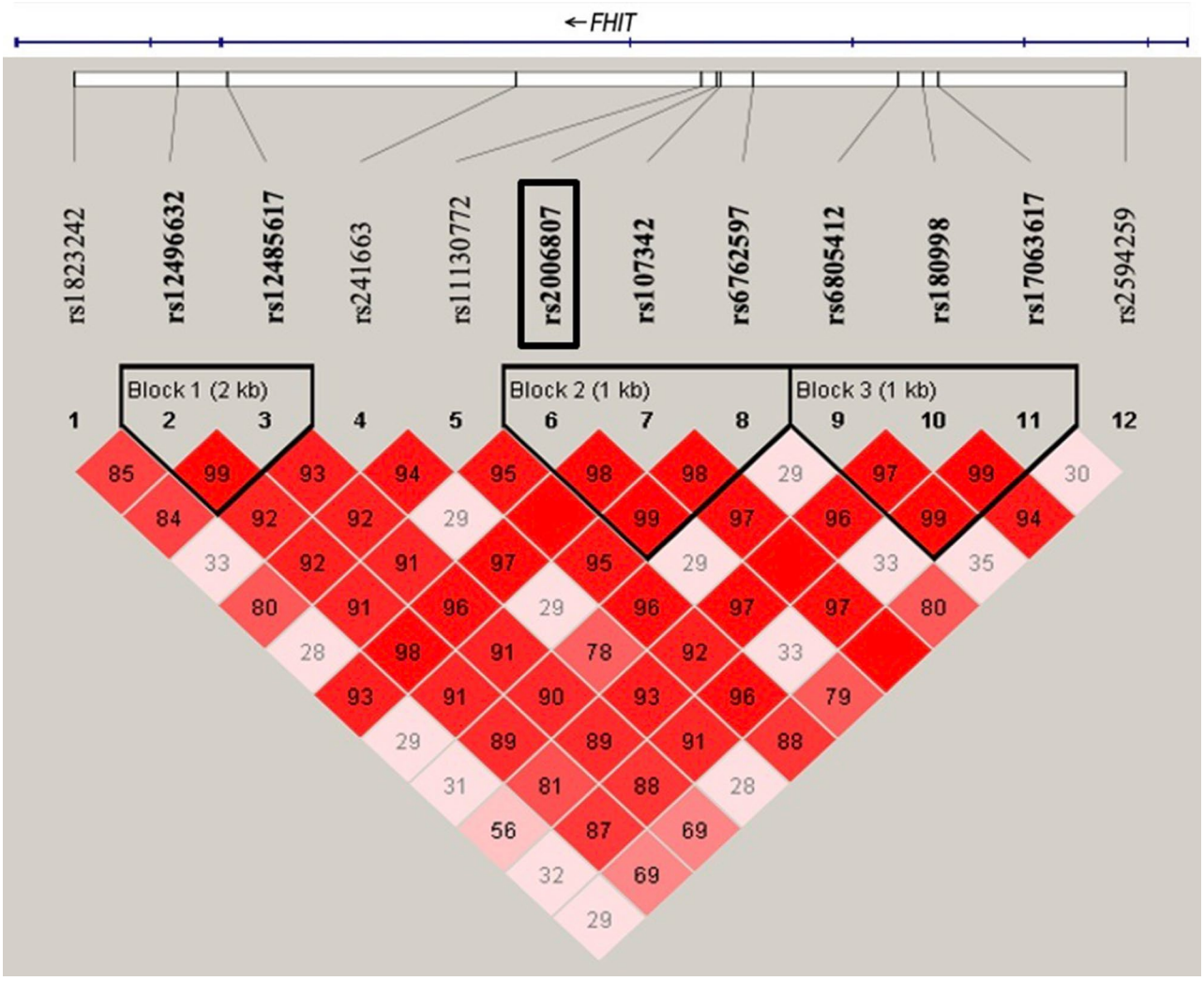

Fig. 5 Linkage disequilibrium (LD) block structure of SNPs in the *FHIT* gene

Table 3 Incidence of metabolic syndrome based on preference for salty foods in Korean adults

Men (*n* = 885)			**Women (*n* = 927)**		
Salty food preference	**HR (95% CI)**	***p*-value**	**Salty food preference**	**HR (95% CI)**	***p*-value**
Crude model					
Dislike	1.00 (Ref.)		Dislike	1.00 (Ref.)	
Like	1.26 (1.02–1.55)	0.0306	Like	1.40 (1.13–1.73)	0.0018
Model 1[1]					
Dislike	1.00 (Ref.)		Dislike	1.00 (Ref.)	
Like	1.26 (1.02–1.56)	0.0297	Like	1.31 (1.07–1.63)	0.0104
Model 2[2]					
Dislike	1.00 (Ref.)		Dislike	1.00 (Ref.)	
Like	1.17 (0.94–1.45)	0.1542	Like	1.12 (0.90–1.39)	0.3063

[1]Adjusted for age; [2]Adjusted for Model 1 plus area, BMI, smoking status, drinking status, education, income, total energy intake, and MET

HR, hazard ratio; CI, confidence interval; BMI, body mass index; MET, metabolic equivalent of task

perception threshold, that is, the more sensitive one is to the salty taste, the lower the risk of developing MetS. However, no significant association was found between the habit of adding salt before tasting food and perceived saltiness [5]. This indicates that an individual's preference for salty taste and actual consumption of salty foods may be inconsistent, which may support our findings. Changes in preferences for saltiness occur as a result of

Table 4 Incidence of metabolic syndrome based on *FHIT* rs2006807 genotypes in Korean adults

Men (*n* = 885)			Women (*n* = 927)		
***FHIT*rs2006807**	**HR (95% CI)**	***p*-value**	**FHIT rs2006807**	**HR (95% CI)**	***p*-value**
Crude model					
AA	1.00 (Ref.)		AA	1.00 (Ref.)	
CC/CA	0.91 (0.75–1.11)	0.3626	CC/CA	1.17 (0.96–1.43)	0.1243
Model 1[1]					
AA	1.00 (Ref.)		AA	1.00 (Ref.)	
CC/CA	0.91 (0.75–1.11)	0.3603	CC/CA	1.18 (0.97–1.44)	0.0993
Model 2[2]					
AA	1.00 (Ref.)		AA	1.00 (Ref.)	
CC/CA	0.93 (0.77–1.14)	0.4955	CC/CA	1.22 (1.00-1.49)	0.0514

[1]Adjusted for age; [2]Adjusted for Model 1 plus area, BMI, smoking status, drinking status, education, income, total energy intake, and MET

FHIT, fragile histidine triad diadenosine triphosphatase, HR, hazard ratio; CI, confidence interval; BMI, body mass index; MET, metabolic equivalent of task

Table 5 Incidence of metabolic syndrome based on salty food preference and *FHIT* genotypes in Korean adults

Variables	Men (*n* = 885)					Women (*n* = 927)				
	Salty food preference					Salty food preference				
	Dislike		Like			Dislike		Like		
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	*p*-interaction	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	*p*-interaction
Crude model										
FHIT rs2006807										
AA	1.00 (Ref.)		1.14 (0.86–1.51)	0.3516	0.3200	1.00 (Ref.)		1.51 (1.11–2.06)	0.0090	0.6104
CC/CA	0.79 (0.56–1.13)	0.1945	1.12 (0.84–1.50)	0.4326		1.30 (0.92–1.85)	0.1357	1.76 (1.28–2.43)	0.0005	
Model 1[1]										
FHIT rs2006807										
AA	1.00 (Ref)		1.14 (0.87–1.51)	0.3465	0.3162	1.00 (Ref.)		1.37 (1.00-1.86)	0.0501	0.9376
CC/CA	0.79 (0.56–1.12)	0.1905	1.12 (0.84–1.50)	0.4293		1.24 (0.88–1.76)	0.2273	1.66 (1.21–2.30)	0.0019	
Model 2[2]										
FHIT rs2006807										
AA	1.00 (Ref.)		1.10 (0.83–1.46)	0.5000	0.5517	1.00 (Ref.)		1.15 (0.83–1.57)	0.4035	0.9743
CC/CA	0.86 (0.60–1.22)	0.3880	1.07 (0.80–1.44)	0.6373		1.23 (0.87–1.76)	0.2455	1.42 (1.03–1.97)	0.0341	

[1]Adjusted for age; [2]Adjusted for Model 1 plus area, BMI, smoking status, drinking status, education, income, total energy intake, and MET

FHIT, fragile histidine triad diadenosine triphosphatase; HR, hazard ratio; CI, confidence interval; BMI, body mass index; MET, metabolic equivalent of task

adaptation to familiarity [43]. Since the saltiness that an individual prefers most in a food is the salt concentration that he or she most frequently consumes, repeated exposure to the same salty food may result in relearning new levels of appropriate saltiness as a result of familiarity [44]. Therefore, salty taste preferences may have changed over the study period and the association with actual food intake may be relative across individuals. This phenomenon may be particularly relevant in the context of Koreans, who frequently consume salted foods such as kimchi, soy sauce, and various pickled fish products [45, 46]. Additionally, the perception of saltiness can be influenced by several other characteristics, including age, smoking, and drinking habits [47].

This study indicated that there was no significant association between the *FHIT* rs2006807 variant alone and the incidence of MetS. To our knowledge, no study to date has directly confirmed the association between the *FHIT* gene variants and MetS. Previous studies have reported that *FHIT* variants are associated with increased risk factors for MetS, such as obesity, diabetes, and hypertension [13, 14, 28]. *FHIT*, a tumor suppressor gene, is involved in apoptosis regulation and cell cycle control [48]. Changes in *FHIT* expression promote tumor progression, and reduced expression is associated with signaling pathways in various cancers [49]. The role of the *FHIT* gene may overlap with the mechanisms driving the components of the MetS. Insulin resistance, chronic

inflammation, and neurohormonal activation are essential factors in the progression of MetS [50], and oxidative stress contributes significantly to these factors [51, 52]. In a study that identified the role of the *FHIT* gene in regulating responses to oxidative and replication stress, it was demonstrated that the absence or mutation of *FHIT* leads to the accumulation of oxidative damage, which can further exacerbate the components of MetS [53]. However, since *FHIT* is primarily involved in DNA repair and response to cellular stress [54], it may not directly affect the major metabolic pathways that drive MetS compared to genetic factors that are closely related to inflammation, insulin signaling, and lipid metabolism [55].

We found that the combined effect of a preference for salty foods and the CA/CC genotype of the *FHIT* rs2006807 variant significantly increased the risk of MetS in women. The *FHIT* gene-taste preference interaction suggests that individuals genetically predisposed to metabolic disturbances due to these variants may be more susceptible to the adverse effects of high salt intake [56]. Potential mechanisms linking gene variants, preferences for salty food, and MetS may involve the regulation of sodium metabolism and inflammatory pathways [56, 57]. The interaction with the *FHIT* gene may influence how individuals respond to high dietary sodium intake, affecting blood pressure regulation, insulin signaling pathways, lipid metabolism, and alterations in hormone levels related to sodium balance, thereby increasing the overall risk of MetS [56, 58, 59]. The effects of the interaction that were observed only in women may be due to sex-specific factors that modulate the genetic and dietary influences on metabolic health. This gender difference may be attributed to hormonal differences and lipid profiles that affect salt sensitivity and blood pressure regulation, as well as differences in health behaviors and dietary patterns between men and women [23, 60–63]. In particular, postmenopausal women may be more susceptible to the effects of high salt intake on blood pressure and metabolic health, which could explain the stronger association observed in this group [64, 65]. In this study, eQTL analysis was conducted using the GTEx database to investigate gene expression levels, and eQTLs for SNP (rs2006807) were identified in the adrenal gland. The AA genotype of rs2006807 was associated with lower expression levels of the *FHIT* gene in the adrenal gland, while the CC genotype was linked to higher expression levels. Previous studies have indicated a relationship between aldosterone, a hormone produced by the adrenal cortex, and MetS. These studies suggest that individuals with MetS tend to have higher plasma aldosterone levels compared to those without the syndrome [66]. High aldosterone levels may exacerbate the risk of metabolic disorders by affecting sodium retention and blood pressure regulation, thus providing additional insights into the mechanisms linking salt intake, *FHIT* alterations, and MetS.

Therefore, considering both genetic and dietary factors in the prevention and management of MetS, particularly in populations with high dietary salt intake, is crucial [5, 59]. Our findings have pivotal implications for healthcare strategies and interventions aimed at tackling the prevalence of MetS. Given the positive relationships between genetic predispositions, dietary preferences, and metabolic health, tailored nutritional guidelines can be developed to mitigate the associated risks and burdens. Such approaches may enhance the effectiveness of dietary interventions aimed at reducing the incidence of MetS, particularly in genetically susceptible populations [7]. Additionally, interventional studies targeting salt intake reduction in high-risk populations are warranted to evaluate the effectiveness of these strategies in preventing and managing MetS.

This study is the first to investigate the effect of the *FHIT* rs2006807 variant on the development of MetS moderated by the preference for salty foods in middle-aged and older Koreans. A prospective cohort design was used to explore the causal relationship between the genetic variant of *FHIT* and preference for salty foods interaction and the development of MetS. In addition, many potential covariates, such as age, area, drinking habits, and smoking status, were controlled to confirm the independent effect of this interaction. Nonetheless, our study has limitations that must be acknowledged. First, the assessment of preference for salty foods may introduce potential bias, as participants may have misreported or inaccurately recalled their dietary habits. Second, the study was conducted in a specific population of middle-aged Korean adults, which may limit the generalizability of the findings to other age groups or ethnic populations. Expanding the research to include other populations and younger cohorts would help to validate these findings and enhance their applicability. Third, given that traditional Korean diets are high in salt [46], the findings may not be directly applicable to populations with different dietary habits and genetic backgrounds. Moreover, while the study focused on the preference for salty foods, it did not account for other dietary factors such as a preference for fat and sugar or the intake of foods rich in these ingredients. These dietary factors may interact in complex ways, contributing to overall cardiometabolic risks [1, 5]. Future research should consider a broader range of dietary preferences and their interactions with genetic factors in the context of MetS. Finally, although our study confirmed the association, it did not elucidate the underlying biological processes linking the *FHIT* variant to MetS. Further studies should explore these biological pathways, particularly in relation to salt

intake, to better understand the gene-diet interactions observed in this study.

Conclusions

In conclusion, this study established a significant combined effect of the *FHIT* rs2006807 gene variant and a preference for salty foods on the development of MetS in middle-aged Korean women. These findings underscore the need for a deeper understanding of how genetic predispositions interact with dietary habits to influence metabolic health. Further research should explore these interactions and the underlying mechanisms of the role of the *FHIT* gene in MetS, as well as confirm these findings in other populations and age groups. In addition, the potential gender contribution to the association between the *FHIT* gene, preference for salty taste, and MetS incidence needs to be elucidated.

Supplementary Information

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Supplementary Material 1

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Author contributions
J.K.: conceptualization, data curation, methodology, formal analysis, writing-original draft, and writing-review and editing. S.L.: methodology, formal analysis, writing-original draft, and writing-review and editing. S.R.A.: writing-original draft. D.S.: conceptualization, data curation, funding acquisition, methodology, supervision, and writing— review and editing. All authors have read and agreed to the published final version of the manuscript.

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Data availability
The Korean Genome and Epidemiology Study (KoGES) data are available through a procedure described at https://biobank.nih.go.kr/cmm/main/mainPage.do (accessed 10 July 2024).

Declarations

Ethical approval and consent to participate
The IRB of Inha University has approved the study (IRB No. 240307–1A), and the participants have given written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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