Genome-wide association study of metabolic syndrome in Korean populations

Seung-Won Oh1, Jong-Eun Lee2*, Eunsoon Shin2, Hyuktae Kwon3, Eun Kyung Choe4, Su-Yeon Choi5, Hwanseok Rhee2, Seung Ho Choi5*

1 Department of Family Medicine, Healthcare System Gangnam Center, Seoul National University Hospital, Seoul, South Korea, 2 DNA Link, Inc., Seoul, South Korea, 3 Department of Family Medicine, Seoul National University Hospital, Seoul, South Korea, 4 Department of Surgery, Healthcare System Gangnam Center, Seoul National University Hospital, Seoul, South Korea, 5 Department of Internal Medicine, Healthcare System Gangnam Center, Seoul National University Hospital, Seoul, South Korea

* These authors contributed equally to this work.
* sw.oh@snu.ac.kr (SWO); cshmed@snuh.org (SHC)

Abstract

Metabolic syndrome (MetS) which is caused by obesity and insulin resistance, is well known for its predictive capability for the risk of type 2 diabetes mellitus and cardiovascular disease. The development of MetS is associated with multiple genetic factors, environmental factors and lifestyle. We performed a genome-wide association study to identify single-nucleotide polymorphism (SNP) related to MetS in large Korean population based samples of 1,362 subjects with MetS and 6,061 controls using the Axiom® Korean Biobank Array 1.0. We replicated the data in another sample including 502 subjects with MetS and 1,751 controls. After adjusting for age and sex, rs662799 located in the APOA5 gene were significantly associated with MetS. 15 SNPs in GCKR, C2orf16, APOA5, ZPR1, and BUD13 were associated with high triglyceride (TG). 14 SNPs in APOA5, ALDH1A2, LIPC, HERPUD1, and CETP, and 2 SNPs in MTNR1B were associated with low high density lipoprotein cholesterol (HDL-C) and high fasting blood glucose respectively. Among these SNPs, 6 TG SNPs: rs1260326, rs1260333, rs1919127, rs964184, rs2075295 and rs1558861 and 11 HDL-C SNPs: rs4775041, rs10468017, rs1800588, rs72786786, rs173539, rs247616, rs247617, rs3764261, rs4783961, rs708272, and rs7499892 were first discovered in Koreans. Additional research is needed to confirm these 17 novel SNPs in Korean population.

Introduction

Metabolic syndrome (MetS) is defined as a cluster of metabolic abnormalities, including abdominal obesity, dyslipidemia, high blood glucose levels, and high blood pressure. Using the definition of the joint scientific statement on MetS [1], its prevalence was 34.2% in US adults and has been reported to increase [2]. In a Korean nationwide survey, 29% of male and 32.9% of female had MetS [3]. MetS is associated with an increased risk of type 2 diabetes, cardiovascular disease, cancer and death [4]. Moreover, individual components of MetS are important risk factors for cardiovascular diseases and are targets for therapeutic intervention. Multiple
genetic loci associated with MetS and its components have been identified by genome-wide association studies (GWAS) [5]. Almost all these loci were reported initially in European ancestry populations, and many studies on Asians have been published recently. However, few such genetic studies have been performed, especially on Koreans. Herein, we conducted a GWAS on a Korean population. The aim of this study was to identify single-nucleotide polymorphism (SNP) that could be associated with MetS components in a Korean population.

Materials and methods

Study subjects

The subjects of our study included Korean adults who had undergone a routine health check-up program in the Seoul National University Hospital Healthcare System Gangnam Center from January 2014 to December 2014. They completed a self-administered questionnaire, which included questions on previous medical history and health related behavior. Patients were excluded from the study when they did not agree to participate in this study, had thyroid functional diseases, took medication or treatment for weight control, or had comorbidity such as myocardial infarction, cerebrovascular diseases, and cancers. After obtaining informed consent, 9,676 individuals donated blood samples, and their blood samples were stored at a biorepository. Anthropometric measurements and laboratory tests were conducted as part of a general health check-up, and genomic DNA was extracted from peripheral blood leukocytes of all participants using the QuickGene DNA whole-blood kit with QuickGene-610 L equipment (Fujifilm, Tokyo, Japan) according to standard protocols. The Institutional Review Board of the Seoul National University Hospital approved the storage of biospecimens with informed consent (IRB number 1103-127-357). We used the biospecimens retrospectively. The board approved this study protocol (IRB number 1504-004-659), and the informed consent was waived by the board.

Biochemical measurements

Eligible participants completed a questionnaire that included demographic factors, comorbidities, and medication for conditions, including hypertension, diabetes mellitus, and hypercholesterolemia. Blood glucose, triglyceride (TG), and high density lipoprotein cholesterol (HDL-C) levels were measured after 12 hours of fasting by using an automated analyzer (Architect c8000; Toshiba Inc., Tokyo, Japan). Height and body weight were assessed after wearing light hospital gowns, and body mass index (BMI) was calculated based on the ratio of body weight to the square of height (kg/m²). Waist circumference (WC) was obtained in the midpoint of the iliac ridge and the lower end of the rib using a measuring tape. An automated sphygmomanometer was used for blood pressure measurement after enough resting time. We used the following criteria for the definition of MetS proposed by the International Diabetes Federation’s criteria for the South Asian ethnic group [6]. MetS was diagnosed if more than 3 of the following indications were present: (1) systolic blood pressure (SBP) ≥ 130 mm Hg or diastolic blood pressure (DBP) ≥ 85 mm Hg or currently on hypertension medication, (2) TG ≥ 150 mg/dL, (3) HDL-C level < 40 mg/dL for men and < 50 mg/dL for women, (4) fasting blood glucose (FBG) level ≥ 100 mg/dL or currently on diabetes medication, and (5) WC ≥ 90 cm for men and ≥ 80 cm for women.

Genotyping and quality control

Genomic DNA was separated from venous blood samples, and 200 ng of genomic DNA was genotyped using Affymetrix Axiom™ KORV1.0–96 Array (Affymetrix, Santa Clara, CA, USA).
The PLINK program (version 1.9; Free Software Foundation Inc., Boston, MA, USA) was used for quality control procedures. Samples matching any of the following criteria were excluded: (1) sex inconsistencies or (2) call rate up to 97%. SNPs were filtered if (1) the call rate was less than 95%, (2) the minor allele frequency was up to 1%, or (3) there was a significant deviation from the Hardy-Weinberg equilibrium permutation test ($P < 1 \times 10^{-4}$). After quality control, 584,061 autosomal SNPs remained for the association analysis. Genotype data were produced using the Korean Chip (K-CHIP) available through the K-CHIP consortium. K-CHIP was designed by Center for Genome Science, Korea National Institute of Health, Korea (4845–301, 3000–3031).

**Statistical analysis**

A total of 584,061 SNPs that passed the quality control was used for GWAS. Baseline characteristics of the study population were presented as mean with standard deviation for continuous variables and number with proportion for categorical variables. We compared the clinical characteristics between subjects with and without MetS using a t-test for continuous variables and a chi-square test for categorical variables. We carried out a case-control study between the individuals with MetS components and without MetS components. Multivariate linear regressions, adjusted for the effects of age and body mass index via an additive model, were used to further investigate the influence of SNPs on Mets components. PLINK software was used for the statistical analysis and to draw the Manhattan plot of $-\log_{10}$. The results were verified using discovery and replication sets. We divided the enrolled population into two groups on the basis of the time of enrollment. Samples enrolled from January 2014 to October 2014 were considered the discovery set ($n = 7,423$), and those enrolled in the subsequent periods were used as the replication set ($n = 2,253$). SNPs that had a $P$-value of less than $10^{-8}$ in the discovery set were re-evaluated for replication. $P$-values less than 0.05 were considered significant in the replication set.

We calculated an inflation factor which was estimated from the mean of the $\chi^2$ tests generated on all SNPs that were tested. The inflation factors in the discovery set were close to 1 for MetS and its components (S1 Table). Principal component analysis (PCA) for our Korean population and 1000 genome phase 3 data revealed the expected ancestry with individuals of east Asian origin (KOR: Korean, CHB: Chinese, JPT: Japanese) which were clustered, those of European origin (CEU) and those of African origin (YRI) (S Fig). Genotype imputation was performed with the software IMPUTE2. 1000 genome phase 3 data was used as a reference panel. Only SNPs imputed with high confidence (Info Score $\geq 0.8$) were chosen for this study. After that, we compared the SNPs which was reported to be related to MetS components in a recent Korean study using Korean Association REsource (KARE) and Health EXAminee (HEXA) cohort data [7] with our results.

**Results**

The mean age of the study subjects was 50.6 years in the discovery set and 51.0 years in the replication set. Table 1 shows the clinical characteristics of the study subjects including the MetS components: BMI, WC, SBP, DBP, fasting glucose, TG, and HDL-C. Among 7,423 in the discovery set, 1,362 (18.3%) were included as MetS cases and among the 2,253 replication set, 502 (22.3%) were included as MetS cases.

After adjusting for age and sex, rs662799 located in the APOA5 gene were significantly associated with MetS in our population ($P = 2.85 \times 10^{-10}$). Association between rs662799 and MetS was maintained in the replication set ($P = 3.19 \times 10^{-3}$) (Table 2). We identified 15 SNPs with a significant influence on hypertriglyceridemia ($\geq 150$ mg/dL). Rs780092, rs780093,
rs780094, rs1260326, and rs1260333 in the *GCKR* gene; rs1919127 and rs1919128 in the *C2orf16* gene; rs662799, rs2075291, and rs2266788 in the *APOA5* gene; rs603446 and rs964184 in the *ZPR1* gene; and rs11216126, rs1558861, and rs2075295 in the *BUD13* gene were associated with hypertriglyceridemia. These 15 SNPs were also validated in the replication set (Table 3). 14 SNPs were associated with low HDL-C (<40 mg/dL for men and <50 mg/dL for women). Rs662799 and rs2075291 in the *APOA5* gene; rs4775041, rs10468017, and rs1800588 in the *ALDH1A2* or *LIPC* gene; and rs7278678, rs173539, rs247616, rs247617, rs3764261, rs4783961, rs708272, rs7499892, and rs2303790 in the *HERPUD1* or *CETP* gene were identified and validated (Table 4). Two SNPs, rs10830962 and rs10830963 in the *MTNR1B* gene, were associated with high FBG (≥100 mg/dL or currently on diabetes medication) (Table 5). Manhattan plot and quantile-quantile plot of the GWAS were drawn using data from discovery and replication set (S2 and S3 Figs). Additionally, rs6589566 in the *ZPR1* gene, which had been previously identified in KARE and HEXA cohort data [7], was also associated with hypertriglyceridemia in the genotype imputation (S2 Table).

### Table 1. Baseline characteristics of the participants.

|                | Discovery set (N = 7423) | Replication set (N = 2253) |
|----------------|--------------------------|----------------------------|
|                | MetS (N = 1362) | No MetS (N = 6061) | P-value | MetS (N = 502) | No MetS (N = 1751) | P-value |
| Age (years)    | 53.5 ± 9.5          | 49.9 ± 10.2             | <0.01   | 52.3 ± 9.5      | 50.6 ± 9.9           | <0.01   |
| Sex (male)     | 1100 (80.8%)        | 3216 (53.1%)            | <0.01   | 408 (81.3%)     | 953 (54.4%)          | <0.01   |
| BMI (kg/m²)    | 26.1 ± 2.8          | 22.4 ± 2.7              | <0.01   | 26.5 ± 2.7      | 22.7 ± 2.7           | <0.01   |
| WC (cm)        | 91.7 ± 6.7          | 80.5 ± 7.8              | <0.01   | 92.9 ± 7.1      | 81.6 ± 7.9           | <0.01   |
| SBP (mmHg)     | 123.9 ± 12.3        | 113.5 ± 12.7            | <0.01   | 124.6 ± 12.7    | 113.8 ± 13.0         | <0.01   |
| DBP (mmHg)     | 83.2 ± 9.1          | 74.3 ± 9.8              | <0.01   | 83.3 ± 9.6      | 74.9 ± 9.7           | <0.01   |
| Fasting glucose| 112.0 ± 21.6        | 95.2 ± 13.5             | <0.01   | 116.0 ± 31.1    | 96.5 ± 13.6          | <0.01   |
| Triglyceride   | 180.7 ± 96.5        | 91.3 ± 53.2             | <0.01   | 181.1 ± 117.6   | 90.5 ± 48.2          | <0.01   |
| HDL-cholesterol| 46.0 ± 9.7          | 55.6 ± 11.9             | <0.01   | 45.2 ± 9.0      | 54.9 ± 11.6          | <0.01   |
| Current smoking| 323 (23.7%)         | 858 (14.2%)             | <0.01   | 107 (21.3%)     | 281 (16.0%)          | <0.01   |
| Alcohol (drink/week) | 15.9 ± 17.1   | 9.6 ± 13.7              | <0.01   | 17.2 ± 19.6     | 9.8 ± 13.7           | <0.01   |
| Physical activity (METS) | 960.7 ± 2011.0 | 936.9 ± 1690.6          | 0.65    | 733.1 ± 1867.4  | 858.8 ± 2266.1       | 0.26    |
| Diabetes medication | 128 (9.4%)  | 119 (2.0%)              | <0.01   | 50 (10.0%)      | 41 (2.3%)            | <0.01   |
| Hypertension medication | 492 (36.1%) | 544 (9.0%)              | <0.01   | 168 (33.5%)     | 145 (8.3%)           | <0.01   |

Values are presented as mean ± standard deviation or number (%). P values are calculated from t-test for continuous variables or from chi-square test for categorical variables. MetS, metabolic syndrome; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high density lipoprotein.

### Table 2. Significant variants associated with metabolic syndrome.

| Chr | SNP    | Position | Gene  | M   | Discovery set | Replication set |
|-----|--------|----------|-------|-----|----------------|-----------------|
|     |        |          |       | MAF | OR (95% CI)   | OR (95% CI)     |
| 11  | rs662799 | 116663707 | APOA5 | G   | 0.345 / 0.288 | 1.346 / 1.476   |
|     |         |          |       |     | 2.85×10⁻¹⁰   | (1.227–1.476)   |

Chr, chromosome; rs number, SNP ID in dbSNP database; M, minor allele; MAF, minor allele frequency; OR, odds ratio; CI, confidence interval, respectively.

https://doi.org/10.1371/journal.pone.0227357.t002
Discussion

We identified SNPs and genomic regions associated with MetS and its components in a Korean population. In this study, 15 SNPs were reported to be associated with TG level. The SNP rs662799 in the APOA5 gene was associated with increased risk of MetS and its components, especially elevated TG and low levels of HDL-C. Two other SNPs in APOA5, rs2266788 and rs2075291, were also associated with elevated TG level. APOA5 gene on chromosome 11q23.3 is known to be associated with dyslipidemia, which is a component of MetS, and a risk of coronary heart disease [5, 8]. A number of SNPs of APOA5 associated with TG and HDL-C levels have been reported [9]. Among these SNPs, rs662799, which is located in the promoter region of the APOA5 gene, was associated with TG levels and coronary heart disease in a Japanese and a Chinese population [10, 11]. Association between rs662799 and elevated TG level...

Table 3. Significant variants associated with hypertriglyceridemia (TG ≥150 mg/dL).

| Chr | SNP   | Position | Gene      | M       | Discovery set | Replication set |
|-----|-------|----------|-----------|---------|---------------|-----------------|
|     |       |          |           |         | (case / control) | (95% CI) | OR | P     | (case / control) | (95% CI) | OR | P     |
| 2   | rs780092 27743154 GCKR G | 0.275 / 0.334 | 0.752 | 4.82×10^{-3} | 0.279 / 0.336 | 0.753 | 1.19×10^{-3} |
|     |       |          |           |         | (0.683–0.827) | (0.635–0.894) |     |       |       |       |     |       |
| 2   | rs780093 27742603 GCKR C | 0.395 / 0.471 | 0.730 | 2.55×10^{-12} | 0.398 / 0.474 | 0.721 | 5.47×10^{-5} |
|     |       |          |           |         | (0.669–0.797) | (0.615–0.845) |     |       |       |       |     |       |
| 2   | rs780094 27741237 GCKR C | 0.397 / 0.472 | 0.736 | 6.49×10^{-12} | 0.400 / 0.475 | 0.723 | 5.91×10^{-5} |
|     |       |          |           |         | (0.674–0.803) | (0.617–0.847) |     |       |       |       |     |       |
| 2   | rs1260326 27730940 GCKR C | 0.385 / 0.460 | 0.731 | 3.89×10^{-12} | 0.392 / 0.463 | 0.729 | 1.07×10^{-4} |
|     |       |          |           |         | (0.669–0.799) | (0.622–0.856) |     |       |       |       |     |       |
| 2   | rs126033 27748624 GCKR C | 0.392 / 0.468 | 0.734 | 5.20×10^{-12} | 0.392 / 0.472 | 0.704 | 1.75×10^{-5} |
|     |       |          |           |         | (0.672–0.802) | (0.600–0.827) |     |       |       |       |     |       |
| 2   | rs191912 27801493 C2orf16 T | 0.417 / 0.477 | 0.776 | 1.18×10^{-8} | 0.420 / 0.491 | 0.755 | 3.67×10^{-4} |
|     |       |          |           |         | (0.711–0.846) | (0.646–0.881) |     |       |       |       |     |       |
| 2   | rs191912 27801759 C2orf16 A | 0.415 / 0.476 | 0.772 | 7.39×10^{-9} | 0.419 / 0.491 | 0.754 | 3.65×10^{-4} |
|     |       |          |           |         | (0.707–0.843) | (0.646–0.881) |     |       |       |       |     |       |
| 11  | rs662799 116663707 APOA5 G | 0.391 / 0.278 | 1.770 | 4.97×10^{-34} | 0.389 / 0.277 | 1.732 | 8.49×10^{-11} |
|     |       |          |           |         | (1.614–1.94) | (1.467–2.045) |     |       |       |       |     |       |
| 11  | rs2075291 116661392 APOA5 A | 0.117 / 0.068 | 1.940 | 3.67×10^{-19} | 0.106 / 0.069 | 1.739 | 6.93×10^{-5} |
|     |       |          |           |         | (1.678–2.243) | (1.324–2.284) |     |       |       |       |     |       |
| 11  | rs2266788 116660686 APOA5 G | 0.273 / 0.209 | 1.482 | 9.26×10^{-15} | 0.281 / 0.207 | 1.538 | 4.03×10^{-6} |
|     |       |          |           |         | (1.342–1.637) | (1.281–1.846) |     |       |       |       |     |       |
| 11  | rs603446 116654435 ZPR1 T | 0.191 / 0.242 | 0.726 | 6.24×10^{-9} | 0.178 / 0.231 | 0.705 | 5.48×10^{-4} |
|     |       |          |           |         | (0.651–0.809) | (0.578–0.860) |     |       |       |       |     |       |
| 11  | rs964184 116648917 ZPR1 G | 0.271 / 0.208 | 1.479 | 1.47×10^{-14} | 0.279 / 0.205 | 1.552 | 2.93×10^{-6} |
|     |       |          |           |         | (1.339–1.634) | (1.291–1.866) |     |       |       |       |     |       |
| 11  | rs2075295 116628401 BUD13 C | 0.404 / 0.466 | 0.755 | 4.56×10^{-10} | 0.424 / 0.480 | 0.793 | 4.04×10^{-3} |
|     |       |          |           |         | (0.691–0.825) | (0.677–0.929) |     |       |       |       |     |       |
| 11  | rs11216126 116617240 BUD13 C | 0.150 / 0.205 | 0.666 | 1.34×10^{-11} | 0.177 / 0.206 | 0.808 | 3.70×10^{-2} |
|     |       |          |           |         | (0.592–0.749) | (0.661–0.987) |     |       |       |       |     |       |
| 11  | rs1558861 116607437 BUD13 C | 0.275 / 0.213 | 1.463 | 5.85×10^{-14} | 0.278 / 0.212 | 1.463 | 4.37×10^{-5} |
|     |       |          |           |         | (1.325–1.616) | (1.219–1.756) |     |       |       |       |     |       |

Chr, chromosome; rs number, SNP ID in dbSNP database; M, minor allele; MAF, minor allele frequency; OR, odds ratio; CI, confidence interval, respectively

https://doi.org/10.1371/journal.pone.0227357.t003
### Table 4. Significant variants associated with low HDL-C (HDL-C level <40 mg/dL for men and <50 mg/dL for women).

| Chr | SNP  | Position | Gene | M   | Discovery set | Replication set |
|-----|------|----------|------|-----|---------------|-----------------|
|     |      |          |      |     | MAF (case / control) | OR (95% CI) | P   | MAF (case / control) | OR (95% CI) | P   |
|     |      |          |      |     | (95% CI)     | (95% CI)     |     | (95% CI)     | (95% CI)     |     |
| 11  | rs662799 | 116663707 | APOA5 | G   | 0.371 / 0.284 | 1.472 | 2.26×10⁻¹⁶ | 0.365 / 0.283 | 1.444 | 9.37×10⁻⁶ |
|     |       |          |      |     | (1.342–1.614) | (1.227–1.699) |     | (1.583–2.633) |     |     |
| 11  | rs2075291| 116661392 | APOA5 | A   | 0.121 / 0.068 | 1.915 | 9.28×10⁻⁹  | 0.124 / 0.065 | 2.042 | 3.89×10⁻⁸ |
|     |       |          |      |     | (1.659–2.209) |     |     | (1.583–2.633) |     |     |
| 15  | rs4775041| 58674695  | ALDH1A2 | C  | 0.167 / 0.217 | 0.717 | 2.28×10⁻⁸  | 0.157 / 0.229 | 0.634 | 8.72×10⁻⁶ |
|     |       |          |      |     | (0.639–0.806) |     |     | (0.519–0.775) |     |     |
| 15  | rs10468017| 58678512 | ALDH1A2 | T  | 0.167 / 0.215 | 0.726 | 7.27×10⁻⁸  | 0.154 / 0.225 | 0.624 | 6.83×10⁻⁶ |
|     |       |          |      |     | (0.646–0.816) |     |     | (0.508–0.767) |     |     |
| 15  | rs1800588| 58723675  | ALDH1A2 | T  | 0.371 / 0.429 | 0.778 | 5.62×10⁻⁸  | 0.375 / 0.414 | 0.842 | 3.45×10⁻³ |
|     |       |          |      |     | (1.342–1.614) |     |     | (1.188–1.748) |     |     |
| 16  | rs72786786| 56985514 | HERPUD1 | A  | 0.132 / 0.185 | 0.663 | 1.65×10⁻¹⁰ | 0.128 / 0.182 | 0.645 | 1.27×10⁻³ |
|     |       |          |      |     | (0.584–0.752) |     |     | (0.516–0.807) |     |     |
| 16  | rs173539 | 56988044  | HERPUD1 | T  | 0.205 / 0.258 | 0.732 | 1.13×10⁻⁸  | 0.219 / 0.262 | 0.796 | 1.38×10⁻² |
|     |       |          |      |     | (0.658–0.815) |     |     | (0.665–0.935) |     |     |
| 16  | rs247616 | 56989590  | HERPUD1 | T  | 0.105 / 0.176 | 0.562 | 1.29×10⁻¹⁶ | 0.113 / 0.177 | 0.587 | 8.36×10⁻⁶ |
|     |       |          |      |     | (0.490–0.644) |     |     | (0.464–0.742) |     |     |
| 16  | rs247617 | 56990716  | HERPUD1 | A  | 0.106 / 0.174 | 0.557 | 7.70×10⁻¹⁷ | 0.113 / 0.175 | 0.594 | 1.38×10⁻⁵ |
|     |       |          |      |     | (0.486–0.639) |     |     | (0.470–0.732) |     |     |
| 16  | rs376426 | 56993324  | HERPUD1 | A  | 0.105 / 0.173 | 0.553 | 5.27×10⁻¹⁷ | 0.112 / 0.173 | 0.598 | 1.97×10⁻⁵ |
|     |       |          |      |     | (0.481–0.635) |     |     | (0.472–0.737) |     |     |
| 16  | rs4783961| 56994894 | HERPUD1 | A  | 0.201 / 0.256 | 0.732 | 9.93×10⁻⁹  | 0.213 / 0.249 | 0.817 | 3.37×10⁻² |
|     |       |          |      |     | (0.657–0.814) |     |     | (0.678–0.985) |     |     |
| 16  | rs708272 | 56996288  | CETP   | A   | 0.337 / 0.395 | 0.777 | 6.09×10⁻⁸  | 0.350 / 0.392 | 0.839 | 3.21×10⁻² |
|     |       |          |      |     | (0.709–0.851) |     |     | (0.715–0.985) |     |     |
| 16  | rs7499892| 57006590 | CETP   | T   | 0.210 / 0.162 | 1.371 | 1.57×10⁻¹⁸ | 0.209 / 0.157 | 1.441 | 2.06×10⁻⁴ |
|     |       |          |      |     | (1.229–1.53)  |     |     | (1.188–1.748) |     |     |
| 16  | rs2303790| 57017292 | CETP   | G   | 0.018 / 0.048 | 0.349 | 5.31×10⁻¹¹ | 0.023 / 0.056 | 0.409 | 1.81×10⁻⁴ |
|     |       |          |      |     | (0.255–0.478) |     |     | (0.256–0.653) |     |     |

Chr, chromosome; rs number, SNP ID in dbSNP database; M, minor allele; MAF, minor allele frequency; OR, odds ratio; CI, confidence interval, respectively.  
https://doi.org/10.1371/journal.pone.0227357.t004

### Table 5. Significant variants associated with high fasting blood glucose (FBG level ≥100 mg/dL or currently on diabetes medication).

| Chr | SNP  | Position | Gene | M   | Discovery set | Replication set |
|-----|------|----------|------|-----|---------------|-----------------|
|     |      |          |      |     | MAF (case / control) | OR (95% CI) | P   | MAF (case / control) | OR (95% CI) | P   |
|     |      |          |      |     | (95% CI)     | (95% CI)     |     | (95% CI)     | (95% CI)     |     |
| 11  | rs10830962 | 92698427 | MTNR1B | G   | 0.473 / 0.423 | 1.277 | 1.15×10⁻¹⁰ | 0.478 / 0.436 | 1.251 | 1.12×10⁻³ |
|     |       |          |      |     | (1.186–1.376) |     |     | (1.093–1.43) |     |     |
| 11  | rs10830963 | 92708710 | MTNR1B | G   | 0.469 / 0.409 | 1.329 | 8.03×10⁻¹⁴ | 0.47 / 0.425 | 1.26 | 6.30×10⁻⁴ |
|     |       |          |      |     | (1.233–1.432) |     |     | (1.104–1.438) |     |     |

Chr, chromosome; rs number, SNP ID in dbSNP database; M, minor allele; MAF, minor allele frequency; OR, odds ratio; CI, confidence interval, respectively.  
https://doi.org/10.1371/journal.pone.0227357.t005
was validated in Koreans [12, 13]. The APOA5 3′-UTR variant, rs2266788, is associated with TG levels through downregulation of APOA5 [14]. This SNP was associated with TG, HDL-C level, and MetS in a European [15] and a Chinese [16] population. In a previous Korean study including 1,193 men, rs2266788 showed marginal association with TG and MetS (P = 0.0027; OR, 1.402) [9]. Rs2075291, a missense SNP in APOA5, is known to be rare in populations of European ancestry. This SNP was associated with HDL-C and TG levels in Chinese and Korean population in previous studies [17, 18].

Other variants of the ZPR1 and BUD13 genes at chromosome 11q23.3 are also known to be associated with serum lipid level. ZPR1, also known as ZNF259, encodes a zinc-finger protein, ZPR1. This protein is essential for the normal nuclear function during cell proliferation. Additionally, the promoter site of ZPR1 binds peroxisome proliferator-activated receptor gamma (PPARG) proteins 1 and 2, which play a key role in insulin sensitivity and obesity [19, 20]. BUD13 is one of the subunits of the RES complex, previously identified in yeast as a splicing factor affecting nuclear pre-mRNA retention [21]. The SNPs rs964184, rs603446, rs2075295, rs11216126, and rs1558861 in ZPR1 and BUD13 gene were associated with elevated TG level in this study. Although the association of the ZPR1 and BUD13 SNPs and serum lipid levels has been reported in the European and Asian population [22, 23], little is known about such an association in Korean populations. In a previous Korean study, rs603446 and rs11216126 were associated with elevated TG and HDL-C level, respectively [24]. However, no previous study has reported the association of rs964184, rs2075295, and rs1558861 with TG levels in Koreans.

In this study, the SNPs rs1260326, rs1260333, rs780092, rs780093, and rs780094 in the GCKR gene were associated with elevated TG level. GCKR at chromosome 2p23.3 encodes the glucokinase regulatory protein (GKRP), which modulates the activity of hepatic hexokinase and, thereby, gates the entry of glucose into the glycolytic and glycogen synthesis pathways. Variants of the gene encoding GKRP were found to have converse effects on TG and glucose metabolic traits [25]. Rs1260326, which is a non-synonymous variant in GCKR, and rs1260333, located downstream of GCKR, were reported to have inverse effects on TG and glucose levels in European descent populations [26–28]. The association between these two SNPs and TG level is validated in Chinese and Japanese [29, 30]. Moreover, TG-increasing alleles of GCKR variants rs1260326 and rs1260333 lowered insulin and HOMA-IR and reduced the risk of insulin resistance in Chinese [31]. The association between rs780092, rs780093, and rs780094 in GCKR and TG levels was also reported in previous European and Asian population studies [25, 32]. In a Korean study, as in our study, major allele carriers of rs780092 and rs780094 in GCKR had significantly higher serum TG levels compared to noncarriers [33]. To our knowledge, the present study is the first to report the effects of GCKR variants rs1260326 and rs1260333 on TG levels in a Korean population. In Korean populations, rs1260326 was associated with the risk of IFG and type 2 diabetes [34] and total and low-density lipoprotein (LDL) cholesterol in children [33]. Rs1919127 and rs1919128 at C2orf16 gene on chromosome 2p23.3 were associated with elevated TG level in our study. Rs1919128 was associated with elevated TG level in a recent Korean study [18]. On the other hand, our study is the first to report that rs1919127 in C2orf16 were associated with elevated TG level in Korean population.

Fourteen SNPs were reported to be associated with HDL-C level in this study. Three SNPs, rs4775041, rs10468017, and rs1800588 were located in ALDH1A2 and LIPC gene on chromosome 15q21.3. ALDH1A2 encodes the protein aldehyde dehydrogenase 1 family member A2. This enzyme catalyzes the synthesis of retinoic acid from retinaldehyde and retinoic acid, the active derivative of vitamin A, is a hormonal signaling molecule that functions in normal organ development [35]. Variants of the ALDH1A2 gene was associated with lipid traits in previous several Asian studies [29, 36]. The LIPC gene provides instructions for making hepatic
Lipase, which helps with the conversion of very low-density lipoprotein (VLDL) to LDL. The enzyme also assists in transporting HDL that carries cholesterol and TG from the blood to the liver. Variants of the LIPC gene are well known to be associated with dyslipidemia [25, 29, 37]. However, our study is the first to report that these 3 SNPs are associated with HDL-C level in Korean. There are relatively few reports on the associations between these polymorphisms and plasma lipid concentrations in Asian individuals. Rs1800588 was associated with low HDL-C level in Chinese population [29, 38]. On the other hand, unlike our study, rs10468017 was not associated with dyslipidemia in another Chinese study, which matched 524 patients with hyperlipidemia with 621 normal subjects [39]. Nine SNPs, rs72786786, rs173539, rs247616, rs247617, rs3764261, rs4783961, rs708272, rs7499892, and rs2303790 are located in the cholesteryl ester transfer protein (CETP) or HERPUD1 gene on chromosome 16q13. CETP is an enzyme responsible for moving cholesterol esters and TG between VLDL, LDL, and HDL. Low CETP levels promote HDL formation. Polymorphisms in the CETP gene, which result in reduced CETP expression, are associated with high plasma HDL-C level and a low prevalence of cardiovascular disease [40]. Of these SNPs, rs3764261 and rs2303790 were associated with HDL level in Japanese [41, 42] and rs708272 was associated with risk of coronary atherosclerosis in Chinese [43]. The association between rs2303790 and low HDL-C was confirmed in a recent Korean study [18]. Our study is the first to report the association between other eight SNPs and HDL-C in Korean.

Two SNPs, rs10830962 and rs10830963 in the MTNR1B gene were associated with high FBG in this study. The MTNR1B gene encodes one of the two known human melatonin receptors, the MT2, and it is highly expressed in beta cells. MTNR1B allele is known to be involved in the regulation of insulin secretion [44]. Previous Korean studies reported the association between rs10830962 and glucose level and gestational diabetes mellitus [45, 46]. Another study reported that rs10830963 was strongly associated with gestational diabetes mellitus in Korean women [47].

In this study, we could not find a SNP that was related to blood pressure in Korean. The mechanism of blood pressure control is not sufficiently explained by the genetic effect, and hypertension is caused by complex interactions between genetic and environmental factors. There have been several Korean studies that examined the interaction between SNPs and environmental factors on the risk of hypertension [48–50]. In this regard, further studies will be necessary.

Few previous studies have evaluated the association between genetic variants and MetS in Korean populations. In 2,657 MetS cases and 5,917 controls among the Korean Genome and Epidemiology study (KoGES) subjects, only two SNPs, rs11216126 and rs180349, were identified with significant p-values ($< 5 \times 10^{-8}$) [51]. Of these two SNPs, rs11216126 is also associated with elevated TG level in our study. Authors of the study emphasized that the multiple correction criteria of conventional GWASs for excluding false-positive loci could simultaneously discard many true-positive loci. In another Korean study, rs662799 of APOA5 was significantly associated with regulated TG levels and MetS, like our study [13]. Participants of this study were only men; however, it was similar to our study in that the participants visited for a routine health check-up. The interaction between this SNP and health-related behaviors was also evaluated in this study, and the SNP showed interactions with alcohol drinking and physical activity. Thus, the results suggested that a strategy of prevention and treatment should be tailored to personal genotype and population. However, we could not evaluate the interaction between environmental and genetic factors. In the recent Korean study using KARE and HEXA cohort data, 21 including five new SNPs were replicated for MetS components [7]. Of these SNPs, rs11216126 and rs2303790 were also associated with TG level and HDL-C level in our study. Additionally, one SNP, rs6589566 in the ZPRI gene was additionally confirmed in
the imputation analysis. Rs6589566 was also associated with TG levels, in Hispanic and Eu-
pean populations [52, 53].

In conclusion, we identified 15 TG SNPs, 14 HDL SNPs, and 2 FBG SNPs in this GWAS. Among these SNPs, 6 TG SNPs: rs1260326 and rs1260333 in GCKR, rs1919127 in C2orf16, rs964184 in ZPR1, and rs2075295 and rs1558861 in BUD13 and 11 HDL SNPs: rs4775041, rs10468017, and rs1800588 in ALDH1A2 and LIPC and rs72786786, rs173539, rs247616, rs247617, rs3764261, rs4783961, rs708272, and rs7499892 in CETP or HERPUD1 were first discovered in Koreans. Additional research is needed to confirm these new SNPs.

Supporting information
S1 Table. Inflation factor for metabolic syndrome and its components in the discovery set. (DOCX)
S2 Table. Association between SNPs identified in a recent Korean study and metabolic syn-
drome components in our study subjects. (DOCX)
S1 Fig. Principal component analysis (PCA) for our Korean population and 1000 genome phase 3 data. (DOCX)
S2 Fig. Manhattan plot for metabolic syndrome components. (DOCX)
S3 Fig. Quantile-quantile plots of the association test results for metabolic syndrome com-
ponents. (DOCX)
S1 Appendix. The questionnaire for study subjects. (DOCX)

Author Contributions
Conceptualization: Seung-Won Oh, Jong-Eun Lee, Hyuktae Kwon, Eun Kyung Choe, Su-
Yeon Choi, Seung Ho Choi.
Data curation: Seung-Won Oh, Eunsoon Shin, Hwanseok Rhee.
Formal analysis: Seung-Won Oh, Jong-Eun Lee, Eunsoon Shin, Hwanseok Rhee.
Funding acquisition: Eun Kyung Choe, Seung Ho Choi.
Investigation: Seung-Won Oh, Jong-Eun Lee, Eun Kyung Choe, Su-Yeon Choi, Seung Ho Choi.
Methodology: Eunsoon Shin, Hyuktae Kwon, Eun Kyung Choe, Hwanseok Rhee, Seung Ho Choi.
Software: Eunsoon Shin, Hwanseok Rhee.
Supervision: Jong-Eun Lee, Seung Ho Choi.
Validation: Eunsoon Shin, Hwanseok Rhee.
Visualization: Eunsoon Shin.
Writing – original draft: Seung-Won Oh, Jong-Eun Lee, Su-Yeon Choi, Seung Ho Choi.
Polymorphisms related to metabolic syndrome

Writing – review & editing: Seung-Won Oh, Jong-Eun Lee, Eunsoon Shin, Hyuktae Kwon, Eun Kyung Choe, Su-Yeon Choi, Seung Ho Choi.

References

1. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation 2009; 120(16):1640–5. https://doi.org/10.1161/CIRCULATIONAHA.109.192644 PMID: 19805654

2. Moore JX, Chaudhary N, Akinyemiju T. Metabolic Syndrome Prevalence by Race/Ethnicity and Sex in the United States, National Health and Nutrition Examination Survey, 1988–2012. Prev Chronic Dis. 2017 Mar 16; 14:E24.

3. Lim S, Jang HC, Lee HK, Kimm KC, Park C, Cho NH. A rural-urban comparison of the characteristics of the metabolic syndrome by gender in Korea: the Korean Health and Genome Study (KHGS). J Endocrinol Invest. 2006 Apr; 29(4):313–9. https://doi.org/10.1007/BF03344102 PMID: 16699297

4. Kaur J. A comprehensive review on metabolic syndrome. Cardiol Res Pract 2014; 2014:943162. https://doi.org/10.1155/2014/943162 PMID: 24711954

5. Povel CM, Boer JM, Reiling E, Feskens EJ. Genetic variants and the metabolic syndrome: a systematic review. Obes Rev. 2011; 12(11):952–67. https://doi.org/10.1111/j.1467-789X.2011.00907.x PMID: 21749608

6. Alberti KG, Zimet P, Shaw J; IDF Epidemiology Task Force Consensus Group. The metabolic syndrome: a new worldwide definition. Lancet 2005; 366:1059–62. https://doi.org/10.1016/S0140-6736(05)67402-8 PMID: 16182882

7. Lee HS, Kim Y, Park T. New Common and Rare Variants Influencing Metabolic Syndrome and Its Individual Components in a Korean Population. Sci Rep. 2018 Apr 9; 8(1):5701. https://doi.org/10.1038/s41598-018-23074-2 PMID: 29632305

8. Maasz A, Kisfalvi P, Horvatovich K, Mohas M, Marko L, Csongei V, et al. Apolipoprotein A5 T-1131C variant confers risk for metabolic syndrome. Pathol Oncol Res. 2007; 13(3):243–7. https://doi.org/10.1007/bf02893505 PMID: 17922054

9. Melegh B, Duga B, Sumegi K, Kisfalvi P, Maasz A, Komlosi K, et al. Mutations of the apolipoprotein A5 gene with inherited hypertriglyceridaemia: review of the current literature. Curr Med Chem. 2012; 19(36):6163–70 PMID: 2350946

10. Takeuchi F, Isono M, Katsuya T, Yokota M, Yamamoto K, Nabika T, et al. Association of genetic variants influencing lipid levels with coronary artery disease in Japanese individuals. Plos One. 2012; 7(9):e46385. https://doi.org/10.1371/journal.pone.0046385 PMID: 23050223

11. Ye HD, Zhou AN, Hong QX, Tang LL, Xu XT, Xin YF, et al. Positive Association between APOA5 rs662799 Polymorphism and Coronary Heart Disease: A Case-Control Study and Meta-Analysis. Plos One. 2015; 10(8).

12. Song KH, Cha S, Yu SG, Yu H, Oh SA, Kang NS. Association of apolipoprotein A5 gene -1131T>C polymorphism with the risk of metabolic syndrome in Korean subjects. Biomed Res Int. 2013; 2013:585134. https://doi.org/10.1155/2013/585134 PMID: 23509746

13. Son KY, Son HY, Chae J, Hwang J, Jang S, Yun JM, et al. Genetic association of APOA5 and APOE with metabolic syndrome and their interaction with health-related behavior in Korean men. Lipids Health Dis. 2015;14.

14. Caussy C, Charriere S, Marcais C, Di Filippo M, Sassolas A, Delay M, et al. An APOA5 3’UTR Variant Associated with Plasma Triglycerides Triggers APOA5 Downregulation by Creating a Functional miR-485-5p Binding Site. Am J Hum Genet. 2014; 94(1):129–34. https://doi.org/10.1016/j.ajhg.2013.12.001 PMID: 24387992

15. Kraja AT, Vaidya D, Pankow JS, Goodarzi MO, Assimes TL, Kullo IJ, et al. A Bivariate Genome-Wide Approach to Metabolic Syndrome STAMPED Consortium. Diabetes. 2011; 60(4):1329–39. https://doi.org/10.2337/db10-1011 PMID: 21366085

16. Shou WH, Wang Y, Xie F, Wang BL, Yang L, Wu H, et al. A functional polymorphism affecting the APOA5 gene expression is causally associated with plasma triglyceride levels conferring coronary atherosclerosis risk in Han Chinese Population. Bba-Mol Basis Dis. 2014; 1842(11):2147–54.

17. Liu ZK, Hu M, Baum L, Thomas GN, Tomlinson B. Associations of polymorphisms in the apolipoprotein A1/C3/A4/A5 gene cluster with familial combined hyperlipidaemia in Hong Kong Chinese. Atherosclerosis. 2010; 208(2):427–32. https://doi.org/10.1016/j.atherosclerosis.2009.08.013 PMID: 19732897
18. 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. https://doi.org/10.1038/s41598-018-3793-9 PMID: 30718733

19. Galcheva-Gargova Z, Gangwani L, Konstantinov KN, Mikrut M, Theroux SJ, Enoch T, et al. The cytoplasmic zinc finger protein ZPR1 accumulates in the nucleolus of proliferating cells. Mol Biol Cell. 1998; 9(10):2963–71. https://doi.org/10.1091/mbc.9.10.2963 PMID: 9763455

20. Corton JC, Anderson SP, Stauber A. Central role of peroxisome proliferator-activated receptors in the actions of peroxisome proliferators. Annu Rev Pharmacol Toxicol. 2000; 40:491–518. https://doi.org/10.1146/annurev.pharmtox.40.1.491 PMID: 10836145

21. Brooks MA, Dziembowski A, Quevillon-Cheruel S, Henriot V, Faux C, van Tilbeurgh H, et al. Structure of the yeast Pml1 splicing factor and its integration into the RES complex. Nucleic Acids Res. 2009; 37(1):129–43. https://doi.org/10.1093/nar/gkn894 PMID: 19033360

22. Johansen CT, Wang JA, Lanktree MB, Cao HN, McIntyre AD, Ban MR, et al. Excess of rare variants in genes identified by genome-wide association study of hypertriglyceridemia. Nat Genet. 2010; 42(8):684–U59. https://doi.org/10.1038/ng.628 PMID: 20657596

23. Nakayama K, Yanagisawa Y, Ogawa A, Ishizuka Y, Munkhtulgaa L, Charupoonphol P, et al. High prevalence of an anti-hypertriglyceridemic variant of the MLXIPL gene in Central Asia. J Hum Genet. 2011; 56(12):828–33. https://doi.org/10.1038/jhg.2011.109 PMID: 21938000

24. Kim YJ, Go MJ, Hu C, Hong CB, Kim YK, Lee JY, et al. Large-scale genome-wide association studies in East Asians identify new genetic loci influencing metabolic traits. Nat Genet. 2011; 43(10):990–5. https://doi.org/10.1038/ng.939 PMID: 21909109

25. Willer CJ, Sanna S, Jackson AU, Scuteri A, Bonnycastle LL, Clarke R, et al. Newly identified loci that influence lipid concentrations and risk of coronary artery disease. Nat Genet. 2008; 40(2):161–9. https://doi.org/10.1038/ng.76 PMID: 18193043

26. Vaxillaire M, Cavalcanti-Proenca C, Dechaume A, Tichet J, Marre M, Balkau B, et al. The common P446L polymorphism in GCKR inversely modulates fasting glucose and triglyceride levels and reduces type 2 diabetes risk in the DESIR prospective general French population. Diabetes. 2008; 57(8):2253–7. https://doi.org/10.2337/db07-1807 PMID: 18556336

27. Perez-Martinez P, Delgado-Listaj A, Garcia-Rios A, Mc Monagle J, GulselaHL, 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. https://doi.org/10.1371/journal.pone.0020555 PMID: 21674002

28. Waterworth DM, Ricketts SL, Song K, Chen L, Zhao J, Ripatti S, et al. Genetic variants influencing circulating lipid levels and risk of coronary artery disease. Arterioscler Thromb Vasc Biol. 2010; 30(11):2264–76. https://doi.org/10.1161/ATVBAHA.109.201020 PMID: 20864672

29. Lu X, Huang J, Mo Z, He J, Wang L, Yang X, et al. Genetic Susceptibility to Lipid Levels and Lipid Change Over Time and Risk of Incident Hyperlipidemia in Chinese Populations. Circ Cardiovasc Genet. 2016; 9(1):37–44. https://doi.org/10.1161/CIRCGENETICS.115.001096 PMID: 26982786

30. Kamatani Y, Matsuda K, Okada Y, Kubo M, Hosono N, Daigo Y, et al. Genome-wide association study of hematological and biochemical traits in a Japanese population. Nat Genet. 2010; 42(3):210–5. https://doi.org/10.1038/ng.531 PMID: 2039978

31. Shen Y, Wu LJ, Xi B, Liu X, Zhao XY, Cheng H, et al. GCKR Variants Increase Triglycerides While Protecting from Insulin Resistance in Chinese Children. Plos One. 2013; 8(1).

32. Spracklen CN, Chen P, Kim YJ, Wang X, Cai H, Li SX, et al. Association analyses of East Asian individuals and trans-ancestry analyses with European individuals reveal new loci associated with cholesterol and triglyceride levels. Hum Mol Genet. 2017; 26(9):1770–84. https://doi.org/10.1093/hmg/ddx062 PMID: 21674002

33. Lee HJ, Jang HB, Kim HJ, Ahn Y, Hong KW, Cho SB, et al. The dietary monounsaturated to saturated fatty acid ratio modulates the genetic effects of GCKR on serum lipid levels in children. Clin Chim Acta. 2015; 450:155–61. https://doi.org/10.1016/j.cca.2015.08.012 PMID: 26291577

34. Kim M, Kim M, Huang L, Lee SH, Lee JH. Genetic risk score of common genetic variants for impaired fasting glucose and newly diagnosed type 2 diabetes influences oxidative stress. Sci Rep. 2018; 8(1):7828. https://doi.org/10.1038/s41598-018-26106-z PMID: 29777116

35. El Kares R, Manolescu DC, Lakhal-Chaieb L, Montpetit A, Zhang Z, Bhat PV, et al. A human ALDH1A2 gene variant is associated with increased newborn kidney size and serum retinoic acid. Kidney Int. 2010 Jul; 78(1):96–102 PMID: 20375987

36. Kim YJ, Go MJ, Hu C, Hong CB, Kim YK, Lee JY, et al. Large-scale genome-wide association studies in east Asians identify new genetic loci influencing metabolic traits. Nat Genet. 2011; 43(10):990–U102. https://doi.org/10.1038/ng.939 PMID: 21909109
37. Kathiresan S, Willer CJ, Peloso GM, Demissie S, Musunuru K, Schadt EE, et al. Common variants at 30 loci contribute to polygenic dyslipidemia. Nat Genet. 2009; 41(1):56–65. https://doi.org/10.1038/ng.291 PMID: 19060906

38. Liu Y, Zhou D, Zhang Z, Song Y, Zhang D, Zhao T, et al. Effects of genetic variants on lipid parameters and dyslipidemia in a Chinese population. J Lipid Res. 2011; 52(2):354–60. https://doi.org/10.1194/jlr.P007476 PMID: 21149302

39. Liu SJ, Zhi H, Chen PZ, Chen W, Lu F, Ma GS, et al. Fatty acid desaturase 1 polymorphisms are associated with coronary heart disease in a Chinese population. Chin Med J (Engl). 2012; 125(5):801–6.

40. Ordovas JM, Cupples LA, Corella D, Otvos JD, Osgood D, Martinez A, et al. Association of cholesteryl ester transfer protein–TaqIB polymorphism with variations in lipoprotein subclasses and coronary heart disease risk: the Framingham study. Arterioscler Thromb Vasc Biol. 2000; 20(5):1323–9. https://doi.org/10.1161/01.atv.20.5.1323 PMID: 10807749

41. Kurano M, Tsukamoto K, Kamitsuji S, Kamatani N, Hara M, Ishikawa T, et al. Genome-wide association study of serum lipids confirms previously reported associations as well as new associations of common SNPs within PCSK7 gene with triglyceride. J Hum Genet. 2016; 61(5):427–33. https://doi.org/10.1038/jhg.2015.170 PMID: 26763881

42. Kanai M, Akiyama M, Takahashi A, Matoba N, Momozawa Y, Ikeda M, et al. Genetic analysis of quantitative traits in the Japanese population links cell types to complex human diseases. Nat Genet. 2018 Mar; 50(3):390–400. https://doi.org/10.1038/s41588-018-0047-6 PMID: 29403010

43. Wang J, Wang LJ, Zhong Y, Gu P, Shao JQ, Jiang SS, et al. CETP gene polymorphisms and risk of coronary atherosclerosis in a Chinese population. Lipids Health Dis. 2013.

44. Prokopenko I, Langenberg C, Florez JC, Saxena R, Soranzo N, Thorleifsson G, et al. Variants in MTNR1B influence fasting glucose levels. Nat Genet. 2009; 41(1):77–81. https://doi.org/10.1038/ng.290 PMID: 19060907

45. Go MJ, Hwang JY, Kim YJ, Oh JH, Kim YJ, Kwak SH, et al. New susceptibility loci in MYL2, C12orf51 and OAS1 associated with 1-h plasma glucose as predisposing risk factors for type 2 diabetes in the Korean population. J Hum Genet. 2013; 58(6):362–5. https://doi.org/10.1038/jhg.2013.14 PMID: 23575436

46. Kwak SH, Kim SH, Cho YM, Go MJ, Cho YS, Choi SH, et al. A genome-wide association study of gestational diabetes mellitus in Korean women. Diabetes. 2012; 61(2):531–41. https://doi.org/10.2337/db11-1034 PMID: 22233651

47. Kim JY, Cheong HS, Park BL, Baik SH, Park S, Lee SW, et al. Melatonin receptor 1 B polymorphisms associated with the risk of gestational diabetes mellitus. BMC Med Genet. 2011; 12:82. https://doi.org/10.1186/1471-2350-12-82 PMID: 21658282

48. Park YM, Kwock CK, Kim K, Kim J, Yang YJ. Interaction between Single Nucleotide Polymorphism and Urinary Sodium, Potassium, and Sodium-Potassium Ratio on the Risk of Hypertension in Korean Adults. Nutrients. 2017; 9(3).

49. Kim SJ, Lee SK, Kim SH, Yun CH, Kim JH, Thomas RJ, et al. Genetic association of short sleep duration with hypertension incidence—a 6-year follow-up in the Korean genome and epidemiology study. Circ J. 2012; 76(4):907–13. https://doi.org/10.1253/circj.cj-11-0713 PMID: 22322875

50. Lim JE, Kim HO, Rhee SY, Kim MK, Kim YJ, Oh B. Gene-environment interactions related to blood pressure traits in two community-based Korean cohorts. Genet Epidemiol. 2019 Feb 15. [Epub ahead of print]

51. Jeong SW, Chung M, Park SJ, Cho SB, Hong KW. Genome-wide association study of metabolic syndrome in Koreans. Genomics Inform. 2014; 12(4):187–94. https://doi.org/10.5808/Gl.2014.12.4.187 PMID: 25705157

52. Coram MA, Duan Q, Hoffmann TJ, Thornton T, Knowles JW, Johnson NA, et al. Genome-wide characterization of shared and distinct genetic components that influence blood lipid levels in ethnically diverse human populations. Am J Hum Genet. 2013 Jun 6; 92(6):904–16. https://doi.org/10.1016/j.ajhg.2013.04.025 PMID: 23726366

53. Wallace C, Newhouse SJ, Braund P, Zhang F, Tobin M, Falchi M, et al. Genome-wide association study identifies genes for biomarkers of cardiovascular disease: serum urate and dyslipidemia. Am J Hum Genet. 2008 Jan; 82(1):159–49. https://doi.org/10.1016/j.ajhg.2007.11.001 PMID: 18179892