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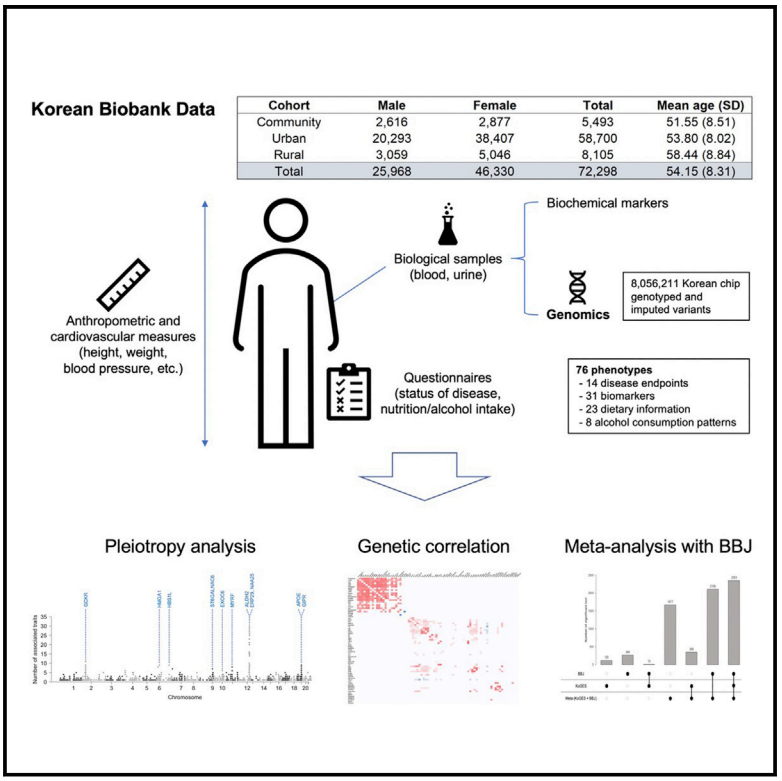
Genome-wide study on 72,298 individuals in Korean biobank data for 76 traits

Graphical abstract



Highlights

- GWAS on individuals in Korean biobank identifies 122 novel associations
- Investigation of pleiotropic genes and genetic correlation across traits
- A meta-analysis including Korean GWAS improves risk prediction accuracy in East Asians

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In brief

Genome-wide association studies (GWAS) on diverse ancestry groups are lacking, resulting in deficits of genetic discoveries. Nam et al. report a GWAS of 76 traits on Korean individuals, identifying 122 novel associations and demonstrating the improvement of the predictive performance of polygenic risk scores by the meta-analysis.

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Genome-wide study on 72,298 individuals in Korean biobank data for 76 traits

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SUMMARY

Genome-wide association studies (GWAS) on diverse ancestry groups are lacking, resulting in deficits of genetic discoveries and polygenic scores. We conducted GWAS for 76 phenotypes in Korean biobank data, namely the Korean Genome and Epidemiology Study (KoGES) (n = 72,298). Our analysis discovered 2,242 associated loci, including 122 novel associations, many of which were replicated in Biobank Japan (BBJ) GWAS. We also applied several up-to-date methods for genetic association tests to increase the power, discovering additional associations that are not identified in simple case-control GWAS. We evaluated genetic pleiotropy to investigate genes associated with multiple traits. Following meta-analysis of 32 phenotypes between KoGES and BBJ, we further identified 379 novel associations and demonstrated the improved predictive performance of polygenic risk scores by using the meta-analysis results. The summary statistics of 76 KoGES GWAS phenotypes are publicly available, contributing to a better comprehension of the genetic architecture of the East Asian population.

INTRODUCTION

Population-based biobanks, such as UK Biobank[2,3] and FinnGen,[4] facilitate genome-wide association studies (GWAS) in tens of thousands or even millions of samples across a large number of traits. These extensive resources helped identify numerous genetic associations and elucidate genetic components of complex traits.[5,6] Using the analysis results, genome-based prediction models have been built and successfully identified individuals with a high risk of disease. Despite the success, a major limitation of the current status of GWAS is the relative lack of non-European samples.[7] As rare variants in Europeans can have high minor allele frequencies (MAFs) in other ancestry groups, the lack of non-European samples can limit further discoveries. In addition, it can cause health disparities if the use of genetic discovery in clinical practice is limited to individuals of European ancestry.[8]

We report a GWAS of 76 phenotypes in 72,298 Korean individuals from the Korean Genome and Epidemiology Study (KoGES), a large biobank conducted by the National Biobank of Korea. Previously several GWAS were performed using KoGES data, including GWAS for anthropometric traits and some metabolites.[9–11] However, these studies mainly focused on one or a few traits of interest. Recently, significant efforts have been made to catalog genetic associations in East Asians by analyzing a large number of phenotypes, including phenome-wide analysis of the Biobank Japan (BBJ)[12–14] and the Taiwan Biobank[15] data. By increasing the sample size and demographic diversity of East Asian GWAS samples, our analysis contributes to novel discoveries. Through the analysis of 14 binary diseases endpoints, 31 biomarkers, 23 dietary information, and 8 alcohol consumption phenotypes, we identified 2,242 associated loci for 47 phenotypes at the genome-wide significance level ($p < 5 \times 10^{-8}$). To fully use the information in the KoGES data, in addition to the mixed effect model for continuous, binary, and categorical phenotypes, we applied up-to-date analysis methods for survival GWAS[16] and methods to incorporate family disease history,[4] and identified 19 additional significant associations. Among associations, 122 were novel, and more than 70% of novel associations with corresponding phenotypes and genetic variants in BBJ were replicated at a nominal p value of 0.05. Many of the novel loci had very low MAFs in Europeans, demonstrating power increment by utilizing samples from diverse ancestry groups.

To find East Asian-specific genetic associations, we conducted meta-analyses for 32 traits using KoGES and BBJ (n = 251,000) GWAS results. We identified 379 novel loci for 25 traits, mostly in clinical biomarkers, and 85% of these loci were not identified in individual studies. We also constructed polygenic risk scores (PRSs) with the meta-analyzed GWAS summary and showed that the PRS trained with the meta-analyzed KoGES and BBJ could have 20% larger R^2 in the prediction of the trait values in East Asian samples in UK Biobank compared with PRSs trained from BBJ GWAS only, demonstrating one potential utility of our analysis results. We publicly provide all GWAS summary statistics to broaden the understanding of the genetic basis of the East Asian population.

RESULTS

KoGES

KoGES, part of the National Biobank of Korea, is a prospective cohort study with a comprehensive range of phenotypic

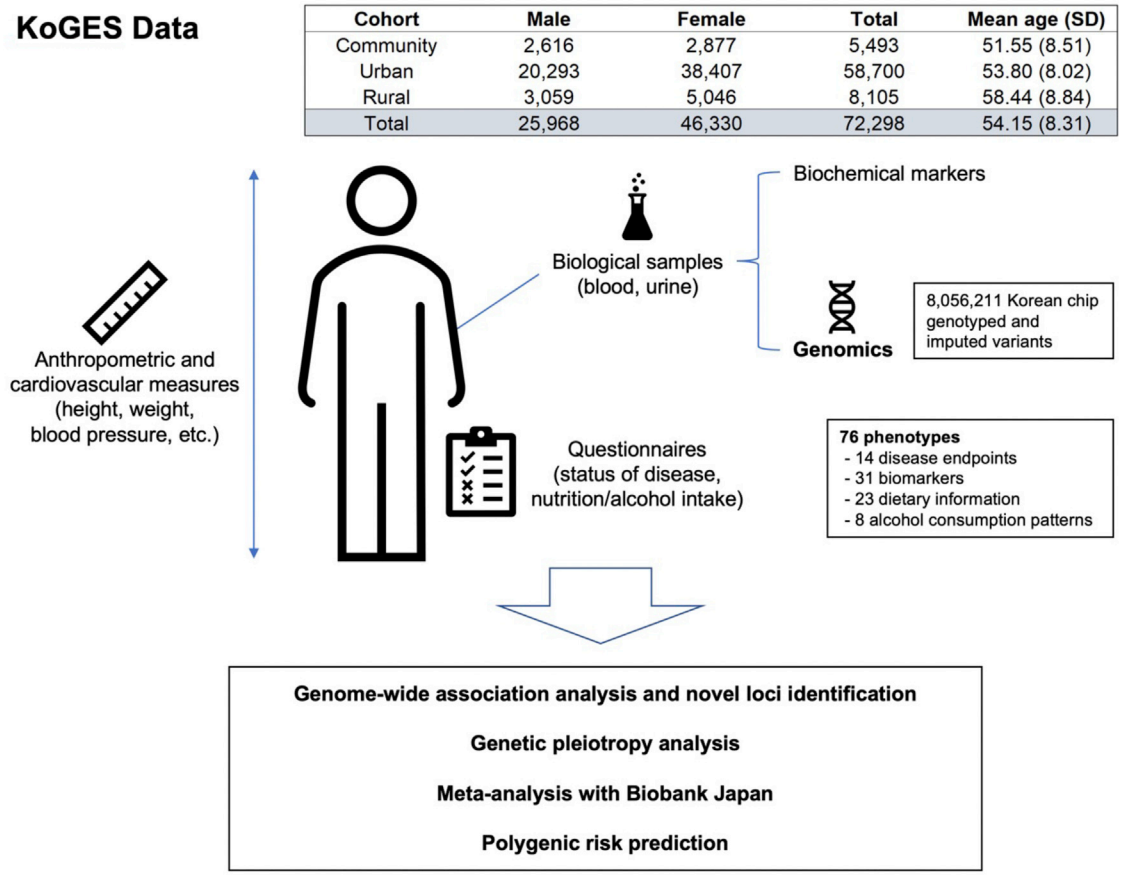

Figure 1. Overview of the KoGES data and our study

KoGES data consist of three cohorts: community-based, urban, and rural cohort. Participants in KoGES are recruited from the national health examinee registry, age ≥40 at baseline. The sample size in the figure indicates the number of samples for which both genotype (after QC) and baseline assessment data exist. See also Table S1.

measures and biological samples, such as DNA, serum, plasma, and urine, collected on approximately 210,000 individuals. KoGES includes the community-based Ansan and Ansung study, the urban community-based health examinee study, and the rural community-based cardiovascular disease association study. Each cohort has the baseline assessment and follow-up measurement thereafter, and we used the baseline measures only in this study (see STAR Methods for details). The table in Figure 1 describes the sample size and the mean age of KoGES data by cohort. A total of 72,000 samples with KoreanChip[17] genotyped and imputed were used in our analysis (see STAR Methods).

GWAS of 76 traits

An overview of our analysis is shown in Figure 1, and the studied traits are described in Table S1. We analyzed 14 binary disease endpoints, 31 biomarkers, 23 dietary information, and 8 traits about alcohol consumption patterns. A total of 8,056,211 genotyped and imputed variants were used in our analysis. For continuous and binary traits, SAIGE[18] was used to maximize power while controlling type I error. For ordinal categorical phenotypes, we applied a proportional odds logistic mixed effect model.[19] A total of 2,223 loci for 47 traits satisfying a genome-wide significance threshold ($p < 5 \times 10^{-8}$) where significant clumped variants are identified using a window width of 5 Mb and a linkage disequilibrium threshold of $R^2 = 0.1$(Table S2). The estimated false discovery rate (FDR) is 0.0017 (FDR = 76 [number of traits] × 10^6 [number of independent loci] × 5 × 10^{-8} [genome-wide significance threshold]/2,223 [number of significant loci]), with assuming 1 million independent loci that correspond to genome-wide $\alpha = 5 \times 10^{-8}$.[20–23] When a more stringent criterion adjusted for the number of phenotypes at the top of the genome-wide significant level ($p < 5 \times 10^{-8}/76 = 6.58 \times 10^{-10}$) was used, the number of significant loci was 1,455 for 42 phenotypes.

We performed linkage disequilibrium score regression (LDSC)[24,25] to estimate heritability and genetic correlation (Table S3). There were no significant confounding biases as the mean LDSC intercept values were 1.0212 for all 76 traits. As expected, height had the largest heritability ($h^2 = 0.400$), followed by weight ($h^2 = 0.270$) and blood platelet count ($h^2 = 0.265$). The estimated heritabilities were similar to those of UKBB and BBJ ($h^2 = 20.402$ and 0.386 for height, respectively). We also computed pairwise genetic correlations to discover the genetic relationship between phenotypes and represented

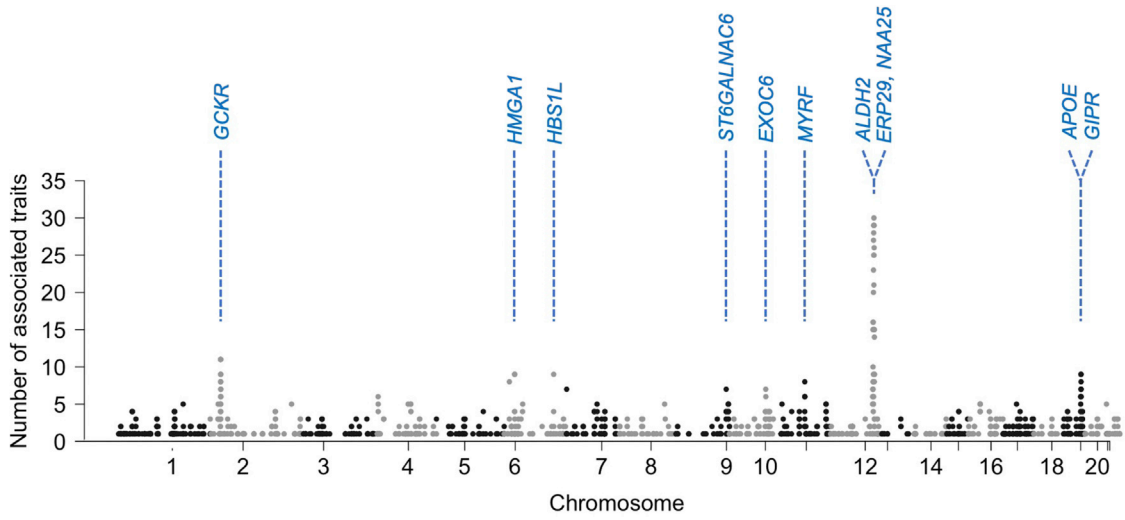

Figure 2. Genetic pleiotropy analysis results

Manhattan plot with the y axis being the number of significantly associated ($p < 5 \times 10^{-8}$) traits per gene for 76 traits in KoGES data. To avoid double-counting the associations in the same phenotypes, results from SPACox and TAPE were excluded when counting the number of significant associations. See also Table S6.

them as a heatmap (Figure S1). To avoid false-positive findings, a genetic correlation was treated as zero when the p value was greater than each threshold. We observed several phenotype clusters with high genetic correlations. Twenty-one phenotypes related to nutrition intake form the largest cluster. In addition, we identified sets of closely related phenotypes, such as (1) liver-related biochemical markers (aspartate transaminase, gamma-glutamyl transpeptidase, and alanine aminotransferase), (2) cardiovascular phenotypes (systolic blood pressure [SBP], diastolic blood pressure [DBP], and hypertension), and (3) hematological traits (hemoglobin, hematocrit, white blood cell count, and red blood cell count).

Using the first onset age, we conducted survival analysis for 14 disease endpoints using SPACox, a method using Cox proportional hazards regression model. We replicated 15 significant associations for 3 traits that were not significant in case-control phenotype analysis. Incidence plots show that these loci influence the disease prevalence (Figure S2). In addition, the association signals identified in case-control GWAS became more significant when applying survival analysis (Table S4).

By incorporating the family disease history, the association test power can be improved. We used the family disease history information of disease endpoints with TAPE.[26] In two types of cancer: gastric cancer and gallbladder cancer, we identified an additional four independent association signals that were not detected in the analysis without family disease history. We calculated the mean value of the TAPE-adjusted phenotypes by the genotype of the top SNP of each locus (Table S5). As the number of minor alleles increases, we observe that the TAPE-adjusted phenotypes monotonically increase or decrease.

Genetic pleiotropy analysis

Since our analysis results show numerous associations, we investigated pleiotropy. To evaluate it at a gene level, we first mapped the most significant variant in each associated locus to a gene using FUMA[27] and then counted the number of phenotypes associated (Table S6). Overall, 826 genes had more than 2 associations. Many genes in chromosome 12 showed high levels of pleiotropy. Two neighboring genes in chromosome 12, *ERP29* (12:112,451,230-112,461,253; GRCh37) and *NAA25* (12:112,464,493-112,546,587; GRCh37), were the most pleiotropic genes with 30 associated phenotypes, and then 8 genes, including *ALDH2*, with 29 associated phenotypes (Figure 2). Except for genes in chromosome 12, *GCKR* in chromosome 2, associated with 11 phenotypes, was the most pleiotropic. *GCKR* encodes glucokinase regulatory protein and is related to many phenotypes affected by glucose metabolisms, such as fasting glucose and insulin measurement.[28] This result is consistent with the studies on other biobank data such as BBJ and UKB.[14]

The number of associated traits per variant is also used to quantify the degree of pleiotropy. Two hundred and sixty-two variants in chromosome 12 were associated with more than 10 traits. Nine variants, including rs671, a missense variant in the *ALDH2* region, were the most pleiotropic variants (27 traits). Except for variants in chromosome 12, rs1260326, a missense variant at the *GCKR* locus (and 12 variants nearby), was the most pleiotropic variant (11 traits).

Novel associations and replications

We identified 122 novel associations for 32 traits among the significant associations (Table S7). We defined the association as a novel if the association is not reported in the GWAS catalog and the p value is not genome-wide significant ($p < 5 \times 10^{-8}$) in the BBJ GWAS (see STAR Methods). Among 122 novel associations, 53 top SNPs for 18 phenotypes were present in BBJ, and 38 SNPs (71.7%) out of 53 had BBJ $p < 0.05$. With a more stringent threshold for replication by Bonferroni correction ($p < 0.05/53 = 9.43 \times 10^{-4}$), 25 top SNPs (47.2%) were replicated. Many of the corresponding variants have low MAFs in

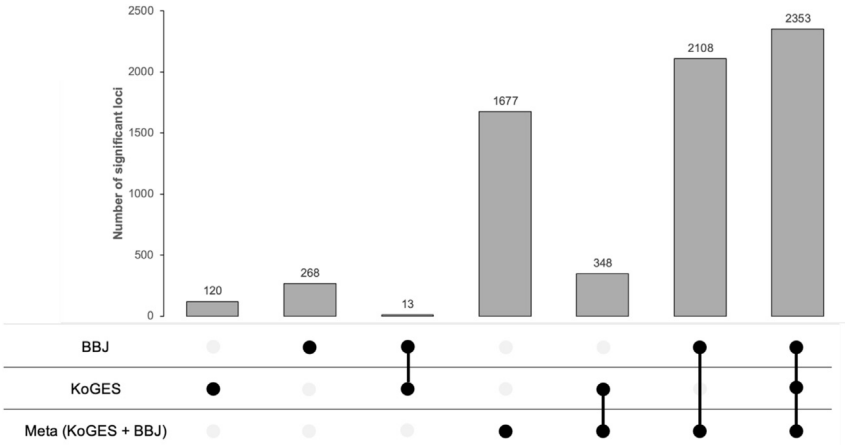

Figure 3. The number of significant associations identified in the KoGES, BBJ, and meta-analysis

Black dots indicate significance in the analysis, and a line connected between dots represents simultaneous significance in multiple cohorts. The number of loci is counted based on the meta-analysis summary statistics after clumping for the variants with p values less than 5×10^{-8}, window size of 5 Mb, and linkage disequilibrium threshold R^2 of 0.1. See also Table S8.

the European population (Figure S3). For example, rs939955, an intergenic variant between *CYP3A4-CYP3A7*, was associated with triglyceride (TG) level ($p = 2.47 \times 10^{-9}$; BBJ $p = 1.2 \times 10^{-4}$). The MAF of rs939955 in KoGES was 0.22, but it was very rare among Europeans ($MAF_{EUR} = 0.002$). Both *CYP3A4* and *CYP3A7* belong to the cytochrome P450 (CYP) superfamily and are well known for drug metabolism. A variant rs1314013, at the *ZEB1* locus, was associated with weight ($p = 7.19 \times 10^{-11}$; BBJ $p = 2.7 \times 10^{-4}$, $MAF_{KoGES} = 0.17$, $MAF_{EUR} = 0.04$). In an experiment on mice, the zinc finger E-box binding homeobox (ZEB1) transcription factor was a repressor of adiposity.[29] A variant rs118190473, at *ANXA3*, was associated with HDL cholesterol level ($p = 4.49 \times 10^{-8}$; BBJ $p = 7.0 \times 10^{-6}$, $MAF_{KoGES} = 0.155$, $MAF_{EUR} = 0.005$). Since adipocyte differentiation and lipid accumulation is the potential function of Annexin A3 (ANXA3),[30,31] our result may provide a link between HDL level and the *ANXA3* locus. *ANXA3* encodes a member of the annexin family and is predicted to be involved in phospholipase A2 (PLA2s) inhibitor activity. Secretory PLA2s are known to be associated with HDL, and a mouse study has shown that overexpression of secretory PLA2 caused the decrease in serum HDL.[32,33] We identified rs9921399, an intron variant at *CES1*, was associated with LDL cholesterol ($p = 1.37 \times 10^{-9}$; BBJ $p = 5.5 \times 10^{-5}$, $MAF_{KoGES} = 0.45$, $MAF_{EUR} = 0.23$). Although this locus has not been demonstrated in GWAS, it is known that LDL cholesterol levels were reduced in carboxylesterase 1-deficient mice.[34] We compared effect sizes and 95% confidence interval for those four loci and drew locus zoom plots (Figure S4).

Meta-analysis with BBJ

To identify genetic associations in the East Asian population, we conducted a meta-analysis for 9 disease endpoints and 23 biomarkers for KoGES together with BBJ and identified 289 genome-wide significant associations for disease endpoints and 6,197 significant associations for biomarkers (Table S8). Figure 3 represents the number of associations identified in the meta-analysis across KoGES and BBJ. As expected, meta-analysis substantially increased the number of significant associations. Of the total 6,486 associated locus-trait pairs, 1,677 (25.8%) were newly identified by the meta-analysis. For example, alanine aminotransferase GWAS identified 26 loci in KoGES and 52 in BBJ, yet 124 loci were significant in the meta-analysis. Among the identified associations, 379 (2 disease associated and 377 biomarker associated) were novel and 321 novel associations were not significant in individual GWAS of KoGES or BBJ.

PRS improvement

We calculated PRSs based on the East Asian meta-analysis GWAS results across KoGES and BBJ and compared them with the BBJ-based and UK-Biobank European-based PRS models. Using PRS-CS,[35] we trained the PRS model for SBP, DBP, high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol, and TGs. To estimate unbiased prediction performance, we used East Asian samples in the UK Biobank as the test samples.

For the five phenotypes we tested, PRS based on the East Asian meta-analysis ($PRS_{EAS\text{-}Meta}$) provided better predictive performance, in terms of R^2, compared with BBJ-based PRS (PRS_{BBJ}) in all models (Table S9A). Interestingly, the European-based PRS model (PRS_{EUR}) performed better than two East Asian-based PRS models (i.e., $PRS_{EAS\text{-}Meta}$ and PRS_{BBJ}) for two blood pressure traits (SBP and DBP). We also conducted a multi-ethnic PRS analysis,[36] which linearly combines PRSs from Europeans and East Asians (Table S9B). For all five phenotypes, the multi-ethnic PRS model based on PRS_{EUR} and $PRS_{EAS\text{-}Meta}$ performed better than the model constructed by PRS_{EUR} and PRS_{BBJ}. To evaluate whether the improvement of the use of $PRS_{EAS\text{-}Meta}$ over PRS_{BBJ} is significant, we fitted the models with $PRS_{EAS\text{-}Meta}$ and PRS_{BBJ} (Table S9C). The first two models included each PRS only, and the third model had both $PRS_{EAS\text{-}Meta}$ over PRS_{BBJ}. When these two PRSs were included in the model, only $PRS_{EAS\text{-}Meta}$ was statistically significant for all five phenotypes we tested. In addition, the R^2 values of the model with two PRSs were not substantially different from the R^2 values of the model with $PRS_{EAS\text{-}Meta}$. This suggests that PRS based on meta-analysis explains the phenotype better than

PRS_{BBJ}. Overall, our analysis result demonstrates that the meta-analysis, including the KoGES GWAS, can contribute to the improvement of risk prediction for East Asians.

DISCUSSION

In this paper, we carried out GWAS for 76 phenotypes in 72,000 Korean samples and identified a large number of significant associations. Our analysis found 122 novel associations previously unknown, and many of them were replicated in BBJ. We also performed pleiotropy analysis and illustrated that the most pleiotropic regions, such as a region of chromosome 12, including *ERP29*, *NAA25*, and *ALDH2*, and a chromosome 2 region, including *GCKR*. Through the meta-analysis with BBJ, we further identified a large number of significant associations. Since most of the novel associations in the meta-analysis with BBJ were not identified in individual GWAS, our study contributes to increasing the effective sample size. We also compared the prediction models based on the meta-analysis results and BBJ summary statistics. We demonstrated that a model based on the meta-analysis across KoGES and BBJ has better prediction performance when predicting trait values for East Asian samples in UK Biobank.

Biobanks collect additional disease information from either surveys or electronic records, such as time to disease onset and family disease history. In addition to genetic association analysis of continuous, binary, and categorical phenotypes, we applied survival analysis (SPACox) and model with family history (TAPE) to utilize time-to-onset age and family history. These methods found 19 more significant loci in 5 traits; all of them were previously known, validating the approach. In addition, many of the significant loci p values were improved. Our analysis demonstrates that time-to-onset and family history are valuable data and can help to identify true associations.

In our pleiotropy analysis, many genes in chromosome 12 were highly pleiotropic and many of the associated phenotypes were related to alcohol consumption. Based on this, it is reasonable to assume that *ALDH2* association with alcohol drives the signals. The variant rs671 in *ALDH2* had a significant negative effect on alcohol consumption and, hence, affected many alcohol-consumption phenotypes and alcohol-related phenotypes, such as blood pressure and cholesterol level. Interestingly, *ERP29* and *NAA25* had an additional association with thyroid disease. *NAA25* is known for its association with hypothyroidism,[37] and both *ERP29* and *NAA25* genes are linked to several traits, including blood pressure and alcohol-related traits.[38]

We acknowledge that the validation rate of novel variants in BBJ was lower than expected, and it did not substantially change even when we applied the Bonferroni corrected threshold. For variants not replicated in BBJ, allele frequencies in KoGES and BBJ were not substantially different. The low validation is probably due to the difference between these two biobanks, such as cohort characteristics, phenotype definition, and measurement.

Although we highlighted the novel loci with low MAF among Europeans, there exist many novel loci that are not rare among Europeans. For example, rs1314013 (MAF_{EUR} = 0.0492) for body weight and rs9921399 (MAF_{EUR} = 0.2646) for LDL cholesterol did not show a signal for association among Europeans (EUR p = 0.75 and 0.17, respectively). This supports the necessity for further investigation of the genetic difference between ancestry groups.

It is not surprising that most dietary-related traits showed a high genetic correlation. In the UK Biobank study,[39] there were several clusters with strong correlations among food-liking phenotypes. Interestingly, we found a negatively strong correlation between sugar intake and retinol (vitamin A1) intake (r_g = −0.90, p = 3.4 × 10^{-7}), both adjusted for overall energy intake. Since there were no genome-wide significant loci for both phenotypes, we could not identify the set of variants or genes to explain this correlation.

We further estimated the heritability of (single) top variants to show the proportion of variance explained by those variants. The single variant heritability can be calculated as $h^2_{GWAS} = \beta^2 \times 2 \times MAF \times (1 - MAF)$, where β is the estimated effect size of the variant and MAF is the minor allele frequencies.[40] For rs939955, a variant associated with TG, h^2_{GWAS} = 4.7 × 10^{-4}; and h^2_{GWAS} = 3.7×10^{-4} for rs118190473, a variant associated with HDLC. These variants only explain the modest amount of heritability compared with the most significant SNPs (h^2_{GWAS} = 0.0193 for rs74368849 with TG and h^2_{GWAS} = 0.0170 for rs72786786 with HDLC). However, it appears to be comparable with other known variants. For example, rs56156922 is associated with TG in both KoGES and BBJ (KoGES p = 9.5 × 10^{-9}; and BBJ p = 1.5 × 10^{-13}), and the heritability explained by it was 4.0 × 10^{-4} and 4.5 × 10^{-4} in KoGES and BBJ, respectively.

For SBP and DBP, European-based PRS showed better prediction performance than East Asian-based PRS. There may be two possible reasons. As the UK Biobank data were used for constructing EUR-based PRS, the phenotype definition and genotyping platform were identical to the test set (East Asians in UK Biobank data), while KoGES and BBJ were not. It is also possible that the genetics of blood pressure may be less varying across ancestry groups than lipid phenotypes. In this case, predictive performance can be more affected by the sample sizes. The EUR-based PRS models were built using GWAS of 400K samples, while sample sizes of BBJ and meta-analysis were 140K and 210K samples, respectively.

To better predict and prevent complex diseases, we need large GWAS in diverse populations. Ideally, GWAS results should be publicly available for meta-analysis and downstream analysis, including novel association identification and replication, PRS calculation, and Mendelian randomization. All our GWAS and meta-analysis results are publicly available on a PheWeb[41] website with interactive visualization of Manhattan, Q-Q, and locus zoom plots. By providing East Asian GWAS on many phenotypes, our results will contribute to elucidating the genetic architecture of complex traits.

Limitations of the study

There are several limitations to our study. First, the disease status phenotypes in KoGES are collected through a self-reported survey and have not been verified by an expert diagnosis. Second, the nutrition intake data in KoGES are derived from a food frequency questionnaire involving 103 foods (see STAR Methods), which can have errors. Third, since there is no

information on medication in KoGES data, calibration of several continuous phenotypes, such as blood pressure, was not feasible. Despite the limitations, our study is the only existing research that analyzed a large number of phenotypes in the Korean population.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

- KEY RESOURCES TABLE
- RESOURCE AVAILABILITY
  - Lead contact
  - Materials availability
  - Data and code availability
- METHOD DETAILS
  - KoGES data
  - GWAS of KoGES data
  - Survival analysis and incorporating family history
  - Gene-level genetic pleiotropy analysis
  - Novel association identification
  - Meta-analysis with biobank Japan
  - PRS evaluation

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.xgen.2022.100189.

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AUTHOR CONTRIBUTIONS

K.N. and S.L. designed the experiments. K.N., J.K., and S.L. analyzed the KoGES data. K.N. and S.L. wrote the manuscript. All authors reviewed and approved the final version of the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
KoGES summary statistics and plots	This paper	https://koges.leelabsg.org https://zenodo.org/record/7042518
Individual-level genotype and phenotype data in KoGES	Moon et al., 2019	4851-302
Biobank Japan summary statistics	Sakaue et al., 2021	https://pheweb.jp/
UK Biobank summary statistics	Pan-UKB team, 2020	https://pan.ukbb.broadinstitute.org/
Software and algorithms		
SAIGE	Zhou et al., 2018	https://github.com/weizhouUMICH/SAIGE
POLMM	Bi et al., 2021	https://github.com/WenjianBI/POLMM
SPACox	Bi et al., 2020	https://github.com/WenjianBI/SPACox
TAPE	Zhuang et al., 2022	https://github.com/styvon/TAPE
LDSC	Bulik-Sullivan et al., 2015	https://github.com/bulik/ldsc
FUMA	Watanabe et al., 2017	https://fuma.ctglab.nl/
PRS-CS	Ge et al., 2015	https://github.com/getian107/PRScs
PLINK	Chang et al., 2015	https://www.cog-genomics.org/plink/2.0/
gwasrapidd	Magno et al., 2020	https://github.com/ramiromagno/gwasrapidd

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the Lead Contact, Seunggeun Lee (lee7801@snu.ac.kr).

Materials availability

This study did not generate new unique reagents.

Data and code availability

The summary statistics generated during this study are submitted to Zenodo: https://zenodo.org/record/7042518. Manhattan plots and quantile-quantile plots generated by the summary statistics are publicly available at https://koges.leelabsg.org. BBJ summary statistics used in this study were downloaded from the Biobank Japan PheWeb: https://pheweb.jp/ and summary statistics for Europeans in UK Biobank were downloaded from Pan-UK Biobank[1]: https://pan.ukbb.broadinstitute.org/. This paper does not report custom code or software. Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

METHOD DETAILS

KoGES data

All samples in the analysis were genotyped with KoreanChip. KoreanChip is a customized array optimized for the Korean population. It has 833K variants selected using 2,576 Korean sequencing data (397 WGS and 2,179 WES). Among them, 600K variants are tagging variants for genome-wide coverage. The details of the KoreanChip can be found elsewhere.[17] We used measures of the baseline recruitment, and only genotyped samples that met the following exclusion criteria were used: low call rate (<97%), excessive heterozygosity, excessive singletons, gender discrepancy, and cryptic first-degree relatives. SNPs with low HWE p value ($<10^{-6}$) or low call rate (<95%) were excluded. After quality control, data were phased using Eagle v2.3 and imputed using IMPUTE4 with 1000 Genomes Project Phase 3 data and the Korean reference genome as a reference panel. Variants with imputation quality score (IQS) < 0.8 and MAF <1% were excluded after imputation. We analyzed 8,056,211 variants in total after these processes.

Anthropometric and clinical measurements in KoGES were obtained by physical examinations and clinical investigations, and the disease status of the participants and family members was collected by the interview. Nutritional intake data were calculated based on a categorical food frequency questionnaire (FFQ) involving 103 foods. The exact sample size and unit of measurement for each

phenotype are described in Table S1. Detailed methods for the measurements, interviews, and questionnaires are described elsewhere.[42,43]

GWAS of KoGES data

For both binary and quantitative traits, we conducted GWAS using a linear mixed model implemented in SAIGE (version 0.44.5) in order to maximize power while controlling type I error for case-control imbalance. In step 1, we used 327,540 variants with Imputation Quality Score (IQS) = 1 to obtain the genetic relationship matrix (GRM). We used the top 10 principal components (PC), age, sex, and adjustment of assessment details such as cohort and year of examination, as covariates in step 1. For quantitative traits, we applied rank-based inverse normal transformation and leave-one-chromosome-out (LOCO) scheme to remove the proximal contamination. For nutrition intake phenotypes, we additionally adjusted for the total energy intake since most nutrients are closely correlated with caloric intake.[44] For ordinal categorical traits, we used a proportional odds logistic mixed model (POLMM) to model the nature of ordinal categorical phenotypes. POLMM is also known to be robust for imbalanced phenotypic distributions, while linear mixed models do not control type I error rate well. After GWAS, we conducted clumping analysis using PLINK2[45] for the variants with p values less than 5×10^{-8}, a window size of 5Mb, and linkage disequilibrium threshold R^2 of 0.1 to count independent genome-wide significant loci. We carried out LD score regression using ldsc (version 1.0.1) to estimate SNP-based heritability, confounding bias, and genetic correlation. All statistical tests from SAIGE and POLMM are two-sided. We reported the results for all 76 studied traits (Table S2).

Survival analysis and incorporating family history

We performed survival analysis for 14 disease endpoints with SPACox (version 0.1.2), a Cox proportional hazards regression model with saddlepoint approximation, using the first onset age in KoGES. We used the same samples and covariates as normal GWAS (top 10 PCs, age, sex, and batch effect). The exact sample size and unit of measurement for each phenotype are described in Table S1.

In KoGES, family disease history data collected by the survey are available. This data indicates whether a family member (separated into paternal, maternal, and siblings) has ever been diagnosed with the disease. With these family disease histories in our data, we conducted an association analysis using TAPE (version 0.2.1). We first adjusted phenotypes (disease status) using three types of family history of disease: paternal, maternal, and siblings for 12 disease endpoints. In TAPE, the adjusted phenotype for individual i (Z_i) is defined as:

$$Z_i = 1(Y_i = 1) + 1(Y_i = 0)\rho \cdot r_i$$

where 1 denotes indicator function, ρ is a pre-specified constant indicating the increase in latent disease risk and $r_i = \frac{\sum_{j=1}^{N_{R_i}} F_{ij} 1(D_{ij} = 1)}{\sum_{j=1}^{N_{R_i}} F_{ij}}$.

In this study, we adjusted phenotypes assuming ρ is equal to 0.5. After adjusting phenotypes, we used the same samples and covariates as normal GWAS (top 10 PCs, age, sex, and batch effect). All statistical tests from SPACox and TAPE are two-sided.

Gene-level genetic pleiotropy analysis

We measured the degree of pleiotropy by counting the number of associated traits (out of 76 traits) per gene and per variant for KoGES GWASs. We excluded the results from survival analysis (SPACox) and model with family history (TAPE) when counting the number of associated traits. For gene-level pleiotropy, we used the SNP2GENE function of FUMA[27] to map SNPs in GWAS results to a gene with 1000 Genome Phase 3 EAS as a reference panel. FUMA is a bioinformatic tool that uses multiple sources of information, including LD structure, functional score, and chromatin interaction, to link associated variants to relevant genes. FUMA first characterizes independent significant variants and surrounding genomic loci based on LD structure. Next, those variants are annotated using various tools and databases such as ANNOVAR,[46] CADD,[47] RegulomeDB,[48] and Hi-C data.[49] Then annotated variants are mapped to genes using position, eQTL association, and chromatin interaction. All parameters used in gene mapping are default values provided by FUMA. For variant-level pleiotropy, we counted the number of associated traits satisfying a genome-wide significance threshold ($p < 5 \times 10^{-8}$).

Novel association identification

We searched for existing associations using the GWAS catalog[50] within ±500 kb from the lead variant to regard an associated locus as novel. In order to screen for variants that have been previously reported, we first used gwasrapidd[51] R package to access the representational state transfer (REST) application programming interface (API) of the GWAS catalog. To map traits reported under different names of traits, we used experimental factor ontology (EFO) traits, and we again exhaustively searched for existing reports of association in the same or similar phenotypes. For example, variants that have been reported for blood-pressure-related traits were excluded from the novel loci for hypertension. Since the results by BBJ[14] were not listed in the GWAS catalog at the time of evaluation for the novel association, we additionally excluded variants that were genome-wide significant in BBJ.

Meta-analysis with biobank Japan

Summary statistics of BBJ were downloaded from the Biobank Japan PheWeb website (https://pheweb.jp/). 9 disease endpoints and 23 biomarker phenotypes were presented in both KoGES and BBJ, and a total of 6,907,490 variants were overlapped in these

two studies. The z-score-based meta-analysis method was used to calculate p values and we used the inverse variance method to obtain the effect sizes for risk prediction. To identify the novel loci, we applied the same criteria as mentioned in the previous section.

PRS evaluation

We calculated polygenic risk scores (PRS) using PRS-CS (version released on June 4, 2021). We used East Asian (EAS) in 1000 Genomes Project phase 3 samples for BBJ-based and meta-analysis-based models and European (EUR) samples for European-based models as the LD reference panel. All parameters used in our analysis are default values provided by PRS-CS software, and we did not specify the global shrinkage parameter phi to use a fully Bayesian approach. The method uses a gamma-gamma prior with a = 1 and b = 0.5. For Markov Chain Monte Carlo (MCMC) in PRS-CS, the total number of iterations is 1,000, the number of burn-in iteration is 500, and thinning factor is equal to 5. When training the PRS models, we used summary statistics after filtering variants that exist in all UK Biobank, KoGES, and BBJ. We additionally restricted variants in HapMap3 as in Prive et al.,[52] so a total of 900,746 variants were used. The effect sizes of the meta-analysis were calculated from inverse variance methods described in the meta-analysis part.

In addition, we conducted a multi-ethnic PRS analysis,[36] which combines PRS from Europeans and East Asians. Multi-ethnic PRS is defined as the linear combination of two PRS: $PRS_{multi} = w_1 PRS_{EUR} + w_2 PRS_{EAS}$. We used half of the East Asian samples in UK Biobank to estimate w_1 and w_2, and the other half was used as a test set. To evaluate the improvement, we compared the significance of PRS in three linear regression models: (1) $Y \sim PRS_{BBJ}$, (2) $Y \sim PRS_{EAS-Meta}$, and (3) $Y \sim PRS_{BBJ} + PRS_{EAS-Meta}$.

Cell Genomics, Volume *2*

Supplemental information

Genome-wide study on 72,298 individuals in Korean biobank data for 76 traits

Kisung Nam, Jangho Kim, and Seunggeun Lee

Supplemental Figures

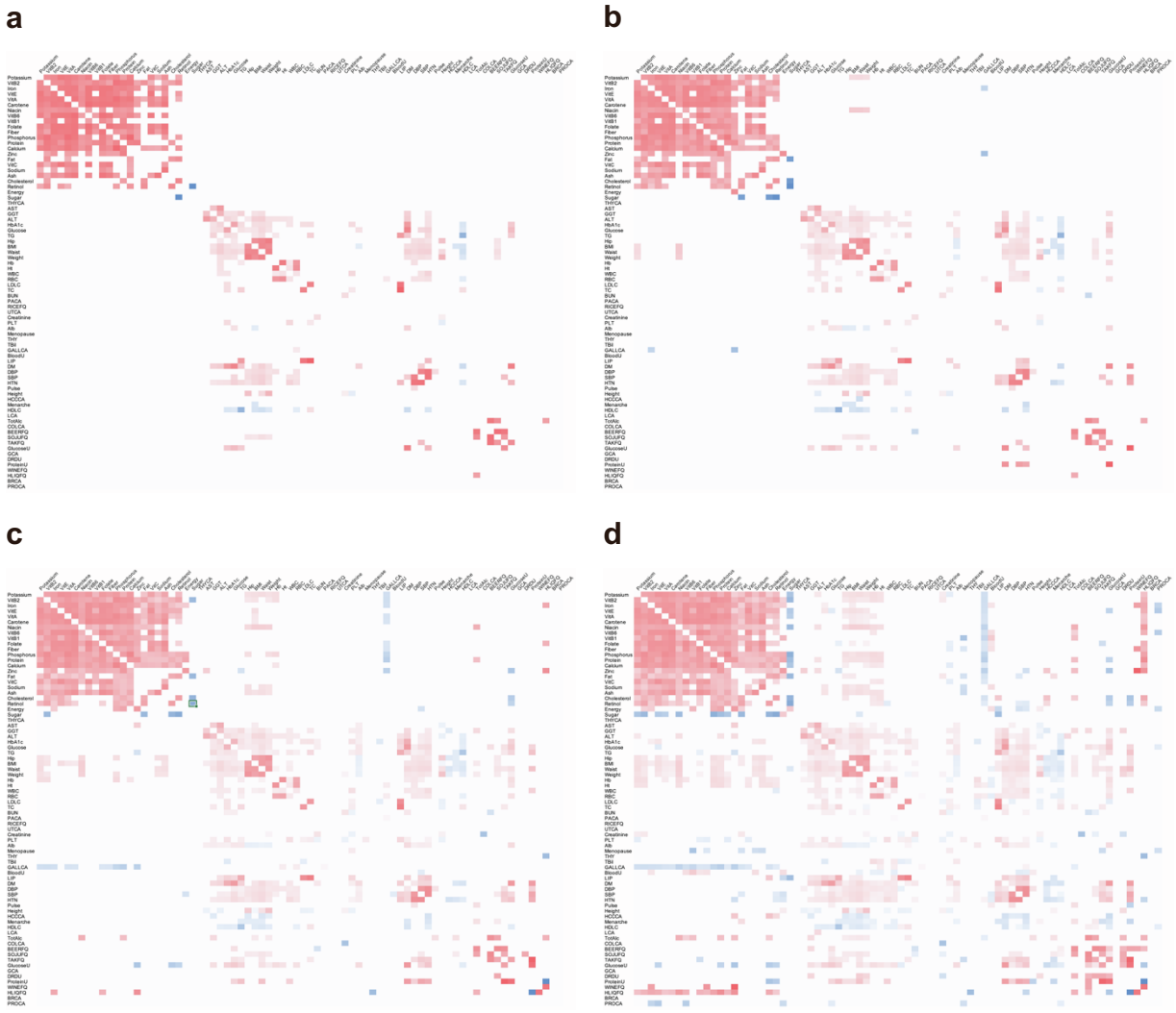
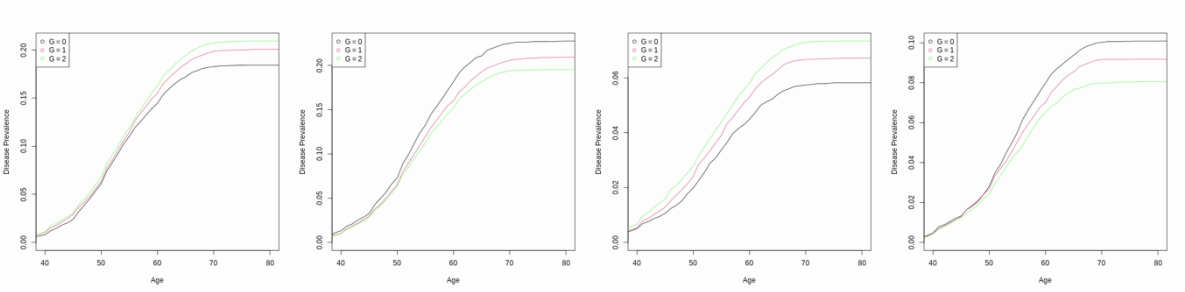


Figure S1: Heatmap for pairwise genetic correlations, Related to STAR Methods. To reduce false positives, genetic correlation was treated as zero when the corresponding p-value is greater than (a) 0.0001, (b) 0.001, (c) 0.01, (d) 0.05, respectively.

a



b

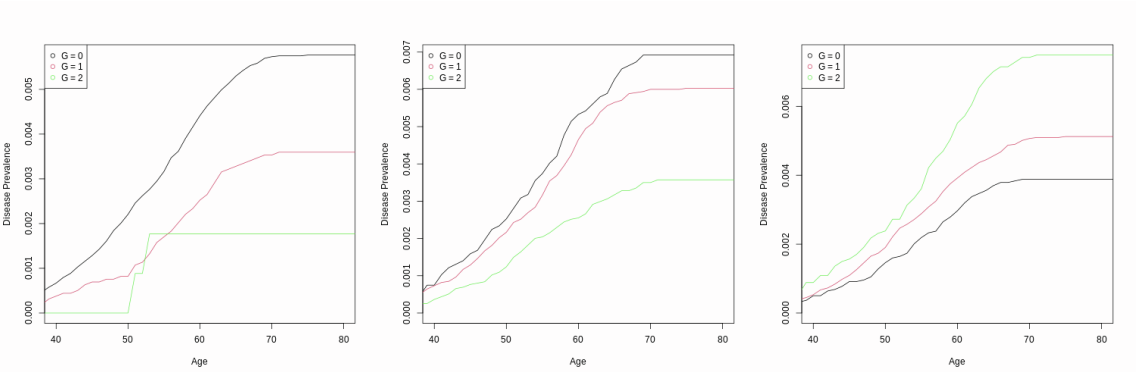


Figure S2: Incidence plot of diseases by genotype of significant variants, Related to STAR Methods. (a) Incidence plot of three disease prevalence by genotype of significant variant. First two plots show the disease prevalence of hypertension (rs71037444 and rs113628671, respectively), and next two plots are of diabetes (rs201174461) and hyperlipidemia (chr16:72,003,267), respectively. (b) Incidence plot of gastric cancer by genotype of most significant loci. Each plot demonstrates the disease prevalence according to the genotype of rs760077, rs2978977, rs866605438, respectively.

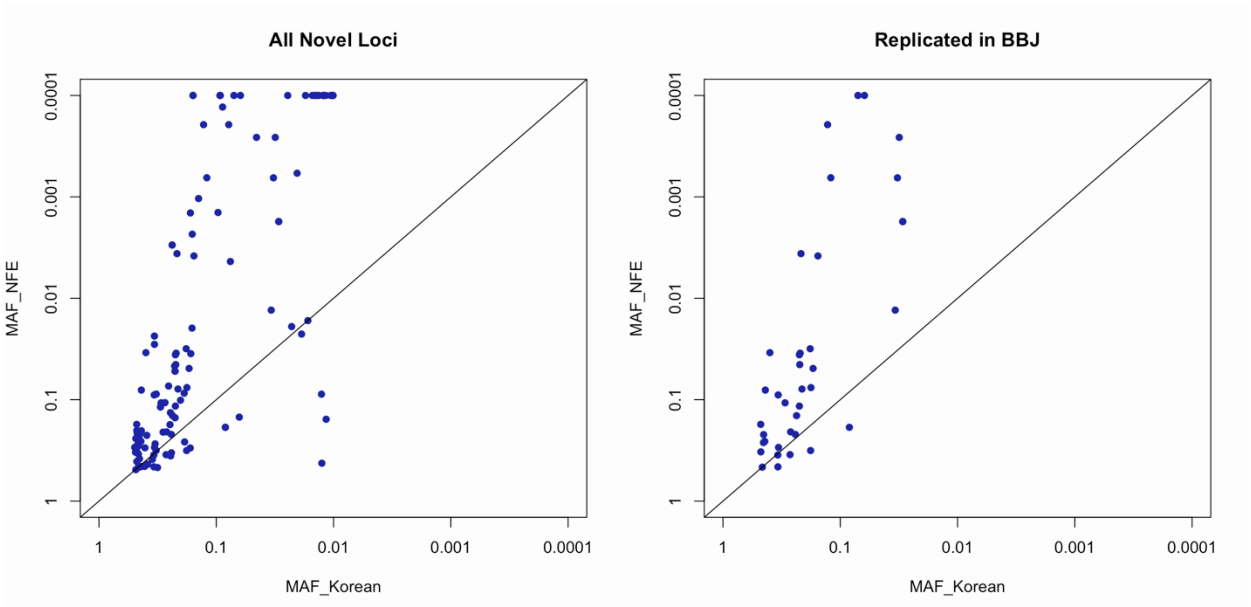
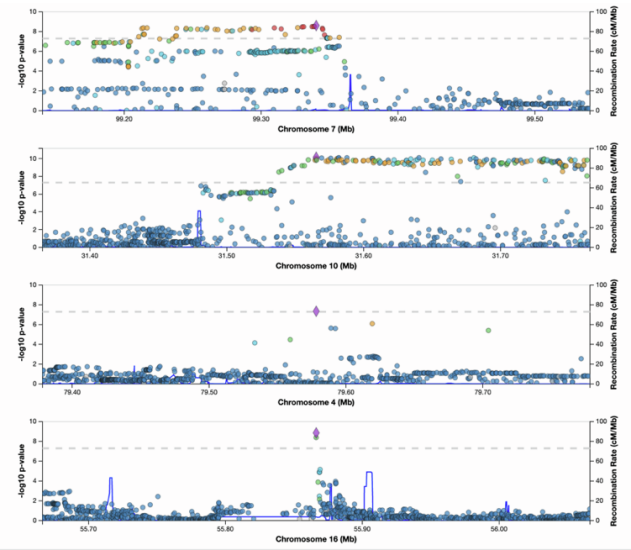


Figure S3: Comparison of minor allele frequencies (MAF) in Korean and non-Finnish European (NFE) for the top variants of 122 novel associations, Related to STAR Methods. MAF estimates in gnomAD were used for NFE. When the MAF is less than 0.0001 or unavailable for NFE, we regarded them as 0.0001 in the plot. 97 variants (79.5%) had lower MAF in NFE than in Korean among all novel loci. After filtering variants replicated in BBJ (p-value less than 0.05 in BBJ), 32 variants (76.3%) had lower MAF in NFE.

a



b

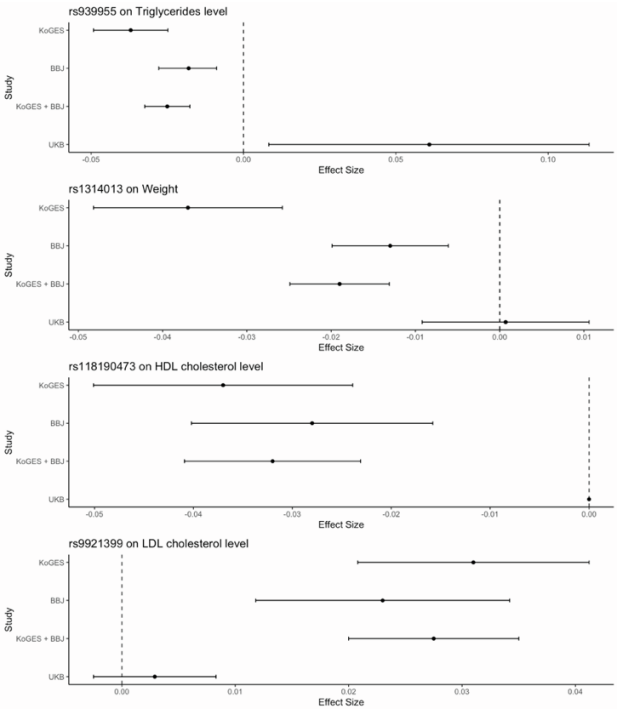


Figure S4: Locus zoom plots and forest plots for selected novel loci, Related to STAR Methods. (a) Locus zoom plots for selected novel loci. (b) Forest plots for effect sizes of top variant of selected novel loci. Each plot represents (1) rs939955 on triglycerides level, (2) rs1314013 on weight, (3) rs118190473 on HDL cholesterol level and (4) rs9921399 on LDL cholesterol level, respectively.

Supplemental Tables

Phenotype	Number of significant loci		Minimum p-value	
	SAIGE	SPACox	SAIGE	SPACox
Hypertension	29	40	3.60E-37	7.20E-40
Diabetes	11	14	9.70E-43	3.80E-46
Hyperlipidemia	11	12	1.00E-24	2.40E-25

Table S4: The number of significant loci and minimum p-value of plain GWAS (SAIGE) and survival analysis (SPACox) for 3 disease endpoints in KoGES data, Related to STAR Methods.

Phenotype	CHR	SNP	Average of adjusted phenotype		
			G = 0	G = 1	G = 2
Gastric cancer	1	rs760077	0.0383 (51,228)	0.0297 (14,552)	0.0299 (1,025)
Gastric cancer	8	rs2978977	0.0421 (9,930)	0.0377 (31,591)	0.0323 (25,284)
Gastric cancer	5	rs866605438	0.0325 (20,174)	0.0362 (33,029)	0.0422 (13,602)
Gallbladder cancer	4	rs75867949	0.008 (376)	0.0028 (9,616)	0.0014 (56,813)

Table S5: The average value of the TAPE-adjusted phenotypes by the genotype of the top SNP of newly found loci by TAPE, Related to STAR Methods. The numbers in parentheses are the sample size of the corresponding group.