1. DESCRIPTION OF PARTICIPATING STUDIES

1.1. Stage 1: GWAS meta-analysis

The Korea Association Resource Study (KARE)

The KARE project has been described previously (1). This project was initiated in 2007 to undertake a large-scale GWAS. A total of 10,038 participants aged between 40 and 69 years were recruited through two population-based prospective cohort studies conducted in the Ansung (n = 5,018) and Ansan (n = 5,020) areas of South Korea. Both cohorts were designed to allow longitudinal prospective studies and adopted the same investigational strategy. More than 260 traits have been extensively examined through epidemiological surveys, physical examinations, and laboratory tests. For this study, we excluded known diabetes, individuals treated with anti-diabetic medicine and individuals with FPG more than 7 mmol/L. Consequently, 7,696 nondiabetic subjects were only tested for FPG.

Genotyping and imputation A total of 10,004 KARE study samples were genotyped using the Affymetrix Genome-Wide Human SNP array 5.0. Genotypes were called using the Bayesian Robust Linear Modeling using the Mahalanobis Distance (BRLMM) algorithm. Samples that exhibited the following properties were excluded: low genotyping calls (< 96%), excessive heterozygosity, sex inconsistency, discordant ethnic membership, or cryptic relatedness. Markers with high missing gene call rates (> 5%), low MAF (< 0.01), or significant deviation from Hardy-Weinberg equilibrium ($P < 1 \times 10^{-6}$) were excluded. Imputation analysis was performed using IMPUTE against all of the HapMap Asian (JPT + CHB) population (release 22/NCBI, build 36, and dbSNP build 126) as a reference panel. We used posterior probability to call the genotype from imputation data and then performed association analyses on imputed data. Of these, SNPs in with a posterior probability score < 0.90, high genotype information content (info < 0.5), HWE ($P < 1 \times 10^{-7}$), and MAF < 0.01 were omitted.

Health Examinee shared control study (HEXA)

The HEXA cohort is one of the Korean Genome and Epidemiology Study (KoGES) population-based cohorts which were initiated in 2001 aiming to identify risk factors of life-style related complex diseases such as type 2 diabetes, hypertension, and dyslipidemia. Approximately 3,700 of 1,200,000 individuals aged 40-69 years from the HEXA cohort were randomly selected as a shared control group for the Korean cancer and coronary artery disease (CAD) GWAS (2). Genotyping was conducted with the Affymetrix Genome-Wide Human SNP array 6.0 in 2008.

Genotyping and imputation A total of 4,302 HEXA study samples were genotyped using the Affymetrix Genome-Wide Human SNP array 6.0. Genotypes were called using the Birdseed algorithm. Samples that exhibited the following properties were excluded: low genotyping calls (< 96%), excessive heterozygosity, sex inconsistency, discordant ethnic membership, or cryptic relatedness. Markers with high missing gene call rates (> 5%), low MAF (< 0.01), or significant deviation from Hardy-Weinberg equilibrium ($P < 1 \times 10^{-6}$) were excluded. Imputation analysis was performed using IMPUTE against all of the HapMap Asian (JPT + CHB) population (release 22/NCBI, build 36, and dbSNP build 126) as a reference panel. We used posterior probability to call the genotype from imputation data and then performed association analyses on imputed data. Of these, SNPs with a posterior probability score < 0.90, high genotype information content (info < 0.5), HWE ($P < 1 \times 10^{-7}$), and MAF < 0.01 were omitted.

Cardiovascular disease Association Study (CAVAS) cohort

Study participants were selected from an ongoing population-based cohort, the Korean Genome and Epidemiology Study (KoGES). Participants were recruited from among residents aged 40-69 years of three rural cities-Yangpyeong in Gyeonggi-do province, Goryeong in Gyeongsangbuk-do province, and

Namwon in Jeollabuk-do province, Korea. A total of 8,702 men and women were recruited from 2004 through 2008 for the baseline study. Of them, 4,052 healthy participants with no history of hypertension, type 2 diabetes, hyperlipidemia, heart disease, blood vessel disease of the brain, or cancer were selected for SNP genotyping.

Genotyping and imputation A total of 4,034 CAVAS study samples were genotyped using Illumina HumanOmni1 Quad v1.0. Genotypes were called using the BeadStudio for CAVAS. Samples that exhibited the following properties were excluded: low genotyping calls (< 98%), excessive heterozygosity, sex inconsistency, discordant ethnic membership, or cryptic relatedness. Markers with high missing gene call rates (> 5%), low MAF (< 0.01), or significant deviation from Hardy-Weinberg equilibrium ($P < 1 \times 10^{-6}$) were excluded. Imputation analysis was performed using IMPUTE against all of the HapMap Asian (JPT + CHB) population (release 22/NCBI, build 36, and dbSNP build 126) as a reference panel. We used posterior probability to call the genotype from imputation data and then performed association analyses on imputed data. Of these, SNPs with a posterior probability score < 0.90, high genotype information content (info < 0.5), HWE ($P < 1 \times 10^{-7}$), and MAF < 0.01 were omitted.

Singapore Prospective study Program (SP2)

The Singapore Prospective Study Program (SP2) is a cross-sectional study of 6,968 adult Singaporean Chinese, Malay and Asian-Indian men and women, aged 24-95 years. Individuals who participated in previous cross sectional studies, the Thyroid and Heart Study 1982–1984 (3), National Health Survey 1992 (4), National University of Singapore Heart Study 1993–1995 (5), or National Health Survey 1998 (6), were invited to participate. All studies involved a random sample of individuals from the Singapore population, aged 24 to 95 years, with disproportionate sampling stratified by ethnicity to increase the number of minority ethnic groups (Malays and Asian Indians). Individuals who were successfully recontacted and gave informed consent answered a questionnaire and attended a clinic examination. Height (m) and weight (kg) were measured similarly in all datasets using standard protocols and were used to derive BMI as weight over height-squared (kg/m²). Institutional review board approval was provided by the National Healthcare Group domain specific review board.

Genotyping and imputation Genotyping assays for the SDCS and SP2 were conducted together as these studies were originally part of a Singaporean Chinese case-control study of type 2 diabetes. A total of 3,066 Chinese adults from the SP2 were genotyped using 1M duo v3 (n = 1,016), Human Hap 610 Quad (n = 1,467), and Hap 550 (n = 583) and 2,210 Chinese adult diabetes cases from the SDCS were genotyped using 1M duo v3 (n = 1,015) and Human Hap 610 Quad (n = 1,195) Beadchips® (http://www.illumina.com/). SiMES Malay adults (n = 3,072) were genotyped using Human Hap 610 Quad arrays.

Duplicate samples were plated for the SDCS and SP2 studies. A total of 8 duplicate samples were available for the SDCS study, while a total of 198 duplicates were available for the SP2 study. The average SNP concordance rate between chips for the post-quality control (QC) duplicated samples was computed based on 531,805 post-QC common SNPs between 1M duo v3 and 610 Quad chips and 496,653 post-QC common SNPs between the 1M duo v3 and 550 chips. The mean concordance was > 95%, and 5 discrepant SNPs were removed (rs10953303, rs11075260, rs1447826, rs274646, and rs430794). For each array in each cohort, a first round of clustering was performed with the proprietary clustering files from Illumina (GenCall). Samples achieving a 99% call rate were subsequently used to generate local cluster files (GenTrain), which were used for a final round of genotype calling. A threshold of 0.15 was implemented on the GenCall score to decide on the confidence of the assigned genotypes.

Samples were removed based on the following conditions: sample call rates of less than 95%, excessive heterozygosity, cryptic relatedness, discordant ethnic membership, or gender discrepancy. Bivariate plots

of sample call rates and heterozygosity, defined as the proportion of heterozygous calls of all valid autosomal genotypes in an individual, were used to assess the overall distribution of missingness and heterozygosity across all the samples. Identity-by-state measures were performed by pair-wise comparison of samples to detect cryptic relatedness such as monozygotic twins, full-sibling pairs, and parent-offspring pairs. One sample from each relationship was excluded from further analysis and where duplicate samples had been genotyped in different SNP-arrays, samples from the denser array was retained. Population structure ascertainment to prevent confounding of study results was performed by using principal component analysis (PCA) with 4 panels from the International HapMap Project (http://hapmap.ncbi.nlm.nih.gov) and the Singapore Genome Variation Project (http://www.nus-cme.org.sg/SGVP) with a thinned set of SNPs to reduce linkage disequilibrium (LD). Individuals who showed ethnic membership discordant from their self-reported ethnicity were excluded from the analysis. For SiMES Malays who showed a continuous cloud suggesting some degree of admixture, the first two principal components were used for correction of population structure in association testing in SiMES. A total of 2,431 SP2 samples, 1,992 SDCS samples, and 2,522 SiMES samples with BMI data were available after sample QC procedures.

We excluded sex and mitochondrial SNPs, together with gross Hardy-Weinberg equilibrium (HWE) outliers (*P*-value $< 1 \times 10^{-4}$). SNPs that were monomorphic or rare (minor allele frequency (MAF) < 1%) and SNPs with low call-rates (< 95%) were also excluded. Where more than one chip was used for genotyping, Mantel-extension tests were carried out to detect differences in allele frequencies of SNPs between the chips; 62 such SNPs were detected in the SP2 and 69 such SNPs were detected in the SDCS and removed from the analyses.

Imputation procedures were performed using IMPUTE v0.5.0. (7) and genotype calls were based on HapMap Phase 1 and 2 East-Asian samples (CHB and JPT) of NCBI build 36 for all Chinese samples (SP2, SDCS). For the Malay samples, all HapMap reference panels (CEU, YRI and JPT + CHB) on NCBI build 36 were used for imputation to better capture local patterns of haplotype variation (8). Actual genotyped calls were placed back into the files and only imputed SNPs, and posterior probability ≥ 0.90 and call-rate $\geq 95\%$ were used.

Shanghai Breast Cancer Study (SBCS)

The SBCS, described in detail elsewhere (9; 10), included two recruitment phases. During the initial phase (SBCS-I), 1,459 breast cancer patients and 1,556 controls were recruited between 1996 and 1998 through a rapid case-ascertainment system and the population-based Shanghai Cancer Registry. Blood samples were obtained from 1,193 (82%) cases and 1,310 (84%) controls. The second phase of participant recruitment (SBCS-II) was conducted between 2002 and 2005 using a protocol similar to the one used during the initial phase. A total of 1,989 incident cases and 1,918 community controls were recruited. The majority of cases (n = 1,932, 97.1%) and controls (n = 1,857, 96.8%) provided a blood sample or an exfoliated buccal cell sample. The age range of participants was 20-70 years with an average age of 50 years.

Shanghai Men's Health Study (SMHS)

The SMHS, described in detail elsewhere (11), is a population-based cohort study of 61,504 Chinese men who were aged between 40 and 74 years, were free of cancer at enrollment, and lived in urban Shanghai, China. Recruitment for the SMHS was initiated in April 2002 and completed in June 2006. A total of 83,058 eligible male residents of eight communities in urban Shanghai were invited to participate by trained interviewers through in-person contact; 61,504 enrolled in the study with a response rate of 74.0%. Reasons for non-participation were refusal (21.1%), out of area during enrollment (3.1%), and other miscellaneous reasons including poor health or hearing problems (1.8%).

All participants of these studies were recruited in Shanghai during the same time period using similar study protocols. Structured questionnaires including the same core questions, were used to collected information on socio demographic factors, reproductive history, lifestyle factors, and dietary habits. Anthropometrics, including weight, height, and waist and hip circumferences were taken by trained interviewers. Blood samples were collected using EDTA-containing BD Vacutainer tubes from study participants at the time of their in-person interview. The lipid profiles were measured using an ACE Clinical Chemistry System. Fasting status was defined as an interval between the last meal and blood draw of 8 hours or longer. A total of 2,017 participants from the SBCS and 291 participants from the SMHS were included in this study.

Genotyping and imputation Genomic DNA was extracted from buffy coats by using a Qiagen DNA purification kit (Valencia, CA) or Puregene DNA purification kit (Minneapolis, MN) according to the manufacturers' instructions and then used for genotyping assays. The GWAS genotyping was performed using the Affymetrix Genome-Wide Human SNP Array 6.0 (Affy 6.0) platform or Illumina 660, following manufacturers' protocols. After sample quality control, we exclude SNPs with MAF < 0.01, call rate < 95%, and concordance rate < 95% among duplicated QC samples. Genotypes were imputed using the program MACH (http://www.sph.umich.edu/csg/abecasis/MACH/download/), which determines the probable distribution of missing genotypes conditional on a set of known haplotypes, while simultaneously estimating the fine-scale recombination map. Phased autosome SNP data from HapMap Phase II Asians (release 22) were used as the reference. To test for associations between the imputed SNP data with BMI, linear regression (additive model) was used, in which SNPs were represented by the expected allele count, an approach that takes into account the degree of uncertainty of genotype imputation (http://www.sph.umich.edu/csg/abecasis/MACH/download/).

The Genetic Epidemiology Network of Salt-Sensitivity (GenSalt) study

GenSalt study participants were recruited from six sites in rural areas of northern China from October 2003 to July 2005 (12). The selection of these study sites was based on the homogeneity of the study population with regard to ethnicity and environmental exposures, including lifestyle, nutritional factors, and habitual dietary intake. The residents in these regions are of the Han ethnicity, the ethnic majority in China. A community-based blood pressure screening was conducted among persons aged 18-60 years in the study villages to identify potential probands and their families for the study. Those with a mean systolic blood pressure between 130-160 mmHg and/or diastolic blood pressure between 85-100 mmHg and no use of antihypertensive medications and their spouses, siblings, and offspring were recruited as volunteers for a dietary intervention study. In general, individuals who had stage-2 hypertension, secondary hypertension, use of antihypertensive medications, history of clinical cardiovascular disease, diabetes, chronic kidney disease, pregnancy, or heavy alcohol use were excluded from the study. A total of 1,906 individuals (1,010 men and 896 women) met the eligibility criteria for the dietary intervention study. Of these individuals, 1,843 (96.7%) completed the entire 21-day dietary intervention and were included in the GWAS. The completeness of the study questionnaire data, blood pressure and anthropometric data, and blood and urine sample collection is near 100%. The institutional review boards at all participating institutes approved the study, and written, informed consent was obtained from each participant.

A standard questionnaire was administered by trained staff at the baseline examination to collect information on demographic characteristics, personal and family medical history, and lifestyle risk factors (including cigarette smoking, alcohol consumption, and physical activity). Three blood pressure measurements were obtained each morning during the 3-day baseline examination by trained and certified observers using a random–zero sphygmomanometer according to a standard protocol. Blood pressure was measured with the participant in a seated position after 5 minutes of rest. In addition, participants were advised to avoid consumption of alcohol, coffee or tea, or cigarettes and exercise for at

least 30 minutes prior to their blood pressure measurements. Body weight, height, and waist circumference were measured twice with the participant in light indoor clothing without shoes. Waist circumference was measured one cm above the participant's navel during minimal respiration. Overnight (≥ 8 hours) fasting blood specimens were obtained for measurement of glucose and lipids. Plasma glucose was measured using a modified hexokinase enzymatic method (Hitachi automatic clinical analyser, model 7060, Japan). Lymphocytic DNA samples were obtained from GenSalt family members (probands, parents, spouses, siblings, and offspring). Genome-wide SNPs were genotyped using Affymetrix® Genome-Wide Human Array 6.0 at the Affymetrix genotyping facility. After removing sex-linked SNPs, mitochondrial SNPs, and 'unassigned' SNPs that had no annotated chromosomal location, 871,166 SNPs were chosen for examination. Strict procedures for extensive QC were used to check the data for any obvious errors, remove uninformative data, and find and remove all Mendelian errors in three stages. In stage 1, we removed participants with gender discrepancies between reported sex and that estimated by PLINK and those who had potential pedigree errors, as determined by GRR (13). In stage 2, we removed monomorphic SNPs, Affymetrix 'housekeeping' SNPs, SNPs with missing rates of >25% or a MAF of <1%. In the final stage, Mendelian errors were found and removed using PLINK (14) and PedCheck (15). After the OC process, 820,015 autosomal SNPs from 1,881 participants remained. An additional 1,792,556 SNPs were imputed from a HapMap reference panel using data on 90 individuals from the JPT and CHB populations. The QC processes removed imputed SNPs with $R^2 < 0.3$, MAF < 1%, Hardy-Weinberg P-value < 10^{-6} , or Mendelian errors. Finally, 2.216.774 autosomal SNPs were used for GWAS analyses.

Cardio-metabolic Genome Epidemiology (CAGE)

The Cardio-metabolic Genome Epidemiology (CAGE) Network is an ongoing collaborative effort to investigate genetic and environmental factors and their interactions affecting cardiometabolic traits/disorders among Asians, including the Japanese (16-18). CAGE participants were recruited in a population-based or hospital-based setting, depending on the design of the member studies. Participation rates varied among the member studies (approximately from 25% in the community-based survey to 80% in the work place-based survey). In the present meta-analysis, 756 population-based Japanese samples were used for preliminary screening of fasting glucose association after excluding individuals with diabetes. These participants were enrolled at two separate sites, the Osaka and Shimane districts. Participants in the Osaka district (n = 390) are part of the Japanese general population cohort samples (19), who have an annual check-up. Participants in the Shimane district (n = 366) are people who visited the Shimane Institute of Health Science for a health screening examination between July 2003 and March 2007. In both populations, we included the participants' data in the test of fasting glucose association, when their blood samples were collected after at least 6 h of fasting.

Genotyping and imputation Genotyping was performed with Infinium HumanHap550 BeadArray (Illumina, San Diego, CA, USA), which interrogated 550K SNPs, according to the manufacturer's protocol. Genotype calling was performed using BeadStudio software (Illumina) and genotype calls with a GenCall Score < 0.53 were dropped from the analysis. QC of SNPs and samples was performed as previously described (18). Briefly, data cleaning and analysis were performed using PLINK software (version 1.06). Among the assayed SNPs, we excluded SNPs for the following reasons: 1) a genotype call rate < 0.95; 2) a significant ($P < 10^{-6}$) deviation from HWE; or 3) MAF, < 0.01. The remaining 451,382 SNPs were analyzed in the genome scan. The average call rate for the 451,382 QC'd SNPs was 99.7% in 756 samples tested for an association with fasting glucose level. Imputation of genotypes to the HapMap Phase 2 (JPT + CHB) set was carried out using BEAGLE software (version 3.0.4).

Cebu Longitudinal Health and Nutrition Survey (CLHNS)

The Cebu Longitudinal Health and Nutrition Survey (CLHNS) is an ongoing community-based birth cohort study that began in 1983 (20). The baseline survey randomly recruited 3,327 pregnant women from the Metropolitan Cebu area, the Philippines in 1983-84 (3,080 singleton live births), and since followed them and their offspring to the present. Trained field staff conducted in-home interviews and collected anthropometric measurements at each visit. Blood samples for biomarker measurement and DNA extraction were obtained in 2005. For this study of 1,779 CLHNS mothers, weight, height, and the calculated BMI were ascertained in the 2005 survey.

Genotyping methods and quality control SNP genotyping, quality control and genotype imputation have been previously described (21). Briefly, SNP genotyping was performed with the Affymetrix Genome-Wide Human SNP Array 5.0, using the standard protocol recommended by the manufacturer. Genotype calling was performed using Birdseed (version 2). The sample call rate was 99.6%. For marker quality control, SNPs with poor mapping, call rate < 90%, and/or deviation from Hardy-Weinberg equilibrium ($P < 10^{-6}$) were removed prior to imputation. We applied a hidden Markov model algorithm implemented in MACH to impute genotypes in CLHNS mother samples based on HapMap (Release 22) JPT + CHB samples. A total of 2,206,824 SNPs with MAF \ge 0.01 and imputation quality Rsq > 0.3 were tested for associations using the software mach2qtl.

Cardiometabolic Risk in Chinese study (CRC)

The Cardiometabolic Risk in Chinese (CRC) Study is a community-based health examination survey of 6,431 individuals (aged 18-93 years; 53.7% men) who were randomly selected from residents living in the urban area of Xuzhou, China in 2009. Written consent was obtained from each participant. The study was reviewed and approved by the ethics committee of the Central Hospital of Xuzhou, Affiliated Hospital of Medical School of Southeast University, Nanjing, China (22; 23).

Genotyping and imputation A total of 811 study samples were included in a GWAS that was carried out on Illumina Human660-Quad Bead Chips at the Chinese National Human Genome Center in Shanghai, China. Genotype clustering was conducted with Illumina BeadStudio 3.3 software. Genotype imputation was performed by each participating study using either MACH. Height was measured to the nearest 0.5 cm without shoes.

The Korean Cancer Prevention Study-II (KCPS-II)

The KCPS-II has been described previously (24). The KCPS-II included 266,258 individuals, aged 20-77 years, who visited 16 health promotion centers across South Korea from April 2004 to December 2008. Participants were interviewed at baseline to obtain exposure data. Cancer diagnoses were identified through 2008 using data from the national cancer registry and hospitalization records. Mortality outcomes were ascertained through 2009 by reviewing death certificates. A computerized search of death-certificate data from the National Statistical Office in Korea was performed using the unique identification number assigned at birth. For the study, we selected 325 CRC patients who provided a blood sample. Cancer-free cohort members (n = 977) were randomly selected as controls. Therefore, a total of 1,302 individuals were genotyped.

Genotyping methods and quality control Cohort samples were genotyped on the Affymetrix Genomewide Human SNP Array 5.0 at DNA Link. For the data obtained from this chip, the following internal quality control (QC) measures were used: the QC call rate (dynamic model algorithm) always exceeded 86%, and the heterozygosity of X chromosome markers was used to identify the gender of each individual. Genotype calling was performed with the Birdseed (v2) algorithm. A total of 1,004 individuals were genotyped via this platform in the first discovery phase. However, 10 of 1,004 individuals were removed because of low genotyping call rates (< 95%). PLINK (v1.07) was used to estimate identity by state (IBS) over all SNPs, and four individuals were shown to be biological relatives, so one member of each pair was excluded. Eleven individuals were also excluded as a result of

gender mismatches. Therefore, 979 individuals were available for this genome-wide analysis. A default set of 400,794 SNPs were used for further analysis, as recommended by Affymetrix. For quality assurance screening, we flagged SNPs with genotype call rates < 95%, minor allele frequencies (MAF) < 0.01, and SNPs showing deviation from Hardy-Weinberg equilibrium (HWE) at P < 0.0001. The final set of acceptable markers included 317,859 autosomal SNPs.

1.2. Stage 2: de novo replication

Health2 cohort

Samples were selected from another community-based cohort provided by the Health2 study. We examined 7,861 individuals selected from the 8,500 participants. The participants were aged 40- 69 years. The study objective and the strategy for clinical measurements of the Health2 cohort were similar to those of the discovery stage participants (1; 2).

Genotyping Genotyping for the Health 2 data carried out by TaqMan (Applied Biosystems Co., Ltd., Foster City, CA).

BioBank Japan

DNA samples were obtained from peripheral blood of individuals enrolled from an annual health checkup conducted at the Hiroshima Atomic Bomb Casualty Council, Health Management Center, National Center for Global Health and Medicine, Keio University or Hiranuma Clinic.

Genotyping Genotyping was performed using multiplex polymerase chain reaction (PCR)-invader assays. Genotyping success rates were > 95 %, and concordance rates examined in selected 188 duplicate samples were 100 %.

The Japanese Millenium Genome Project (JMGP)

JMPG comprises 7 independent study cohorts for studies of cardiovascular diseases and related risk factors. The Ohasama study of Tohoku University, the Shigarakiand Takashima studies of Shiga University of Medical Science, and the Nomura study and Toon health study of Ehime University are general population-based genetic epidemiological studies of subjects recruited via a medical check-up process for community-residents. The Yokohama (Yokohama City University) and Matsuyama (Ehime University) cohorts are derived from employees of large manufacturing industries located in Kanagawa and Matsuyama City, Ehime Prefecture (western part of Japan), respectively. In all cohorts, clinical parameters were obtained from personal health records during the annual or biennial medical check-up process.

Genotyping Samples were genotyped using the TaqMan assay (Applied Biosystems by Life Technologies, Carlsbad, CA). A total 10,299 participant whom fasting plasma glucose data and genotyping results were available were included in the replication analysis.

Shanghai Jiao Tong University Diabetes Study (SJTUDS)

The subjects were selected from Shanghai Diabetes Study I and II, which were community-based random sample epidemiological studies of diabetes and related metabolic disorders. All subjects (n = 3,412) were Chinese Hans with normal glucose tolerance as assessed by a standard 75 g oral glucose tolerant tests (OGTTs), and negative family history of diabetes. Phenotypes for anthropometric and biochemical traits related to glucose metabolism were measured. OGTTs were performed in the morning after an overnight fast. Blood samples were obtained at the fasting and 2 h during OGTTs. Plasma glucose and serum insulin were measured. Basal insulin sensitivity and beta cell function were calculated from fasting plasma glucose and insulin using HOMA.

Genotyping The SNPs were genotyped using primer extension of multiplex products with detection by matrix-assisted laser desorption ionization-time of flight mass spectroscopy using a Mass ARRAY Compact Analyzer (Sequenom, San Diego, CA, USA). After quality control, 3,300 subjects were included into the final analysis.

Chinese University of Hong Kong Diabetes Study (CUHKS)

The study design, ascertainment, inclusion criteria and phenotyping of the study subjects have been described previously (25; 26). All subjects were of southern Han Chinese ancestry residing in Hong Kong. This study cohort consists of 474 adults (44.9% male, mean age 41.8 ± 8.9 years, mean BMI 23.1 \pm 3.4 years) with FPG < 6.1 mmol/l recruited from hospital staff and volunteers from a community-based health screening program. This study was approved by the Clinical Research Ethics Committee of the Chinese University of Hong Kong. All participants gave written informed consent as appropriate. *Genotyping* Genotyping was performed using primer extension of multiplex products with detection by MALDI-TOF mass spectroscopy on a Sequenom MassARRAY platform (San Diego, CA, USA).

2. SUPPLEMENTARY FIGURES AND TABLE LEGENDS.

Supplementary Figure 1. Overall study work flow.



Supplementary Figure 2. Quantile-quantile plot for FPG. The observed *P*-values (y axis) were compared with the expected *P*-values under the null distribution (x axis) for FPG. The expected null distribution is plotted along the black diagonal. The entire distribution of observed *P*-values is plotted in red. The distribution after excluding the previously reported FPG loci is plotted in blue. The distribution after excluding all known and new loci is plotted in green.





Supplementary Figure 3. Gene relationships among implicated loci (GRAIL)-VIZ plot of functional connections.

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Supplementary Table 1. Descriptive characteristics of cohort studies

Supplementary Table 2. Information for genotyping, Imputation and association analysis

Supplementary Table 3. Association results of stage 1 meta-analysis for established FPG loci

Supplementary Table 4. Evidence of association of 3 new loci with fasting plasma glucose in Europeans from the MAGIC consortium

Supplementary Table 5. Associations for two KANK1 variants with glucose and proinsulin levels in 8,633 METSIM samples

Supplementary Table 6. Association of SNPs rs10815355 and rs3824420 with insulin-related traits such as fasting insulin and homeostatic model for assessment of beta-cell function (HOMA-B) in KARE study

Supplementary Table 7. Comparison of SNP minor allele frequency and linkage disequilibrium among ethnic groups

Supplementary Table 8. Conditional analyses for SNPs, rs10815355 and rs3824420. Association analysis of one SNP for fasting glucose was adjusted with the other SNP.

Supplementary Table 9. Conditional analyses for fasting glucose SNPs. The association of SNPs with fasting glucose was adjusted with insulin-related traits.

Supplementary Table 10. Genetic association of 3 new FPG loci with type 2 diabetes. Results of type 2 diabetes association were obtained from AGEN-T2D consortium.

Supplementary Table 11. List of regions contained in the 43 loci identified by genome-wide association meta-analysis (using published PubMed abstracts prior to December, 2006) with the gene identified by GRAIL analysis. GRAIL P_{Region} -value column presents the best significant P_{Gene} -value adjusted for the multiple comparisons within a locus with at least one gene. The right panel presents the keywords over-described in PubMed abstracts featuring the most connected genes functionally.

Supplementary Table 12. List of connection results from the GRAIL analysis for selected genes ($P_{\text{Gene}} < 0.05$) in Supplementary Table 11. GRAIL P_{Gene} -values are the results for the test of the gene itself, and thus are not adjusted for the number of genes tested within a locus. Analysis results present connections between previously known fasting glucose associated genes based on their prior literature.

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