SUPPLEMENTARY DATA

Cohort descriptions

Stage 1 cohorts

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. The study design has been described elsewhere [1]. 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. A total of 811 study samples were included in a GWAS that was carried out on Illumina Human660-Quad BeadChips at the Chinese National Human Genome Center in Shanghai, China. Genotype clustering was conducted with Illumina BeadStudio 3.3 software. Fasting glucose was measured using the hexokinase glucose-6-phosphate dehydrogenase method (Type 7600; Hitachi Ltd., Tokyo, Japan). HbA_{1C} was measured using high performance liquid chromatography (HPLC; HLC-723G7 hemoglobin HPLC analyzer). The top 10 PCs and age were included as covariates in addition to the sex and BMI.

Korea Association Resource (KARE) is a part of the Korean Genome Analysis Project (KoGAP), was initiated in 2007 to conduct a large-scale genome-wide association study aiming to discover variants associated with Type 2 Diabetes (T2D) and numerous complex traits. The detailed information has been described elsewhere[2]. Briefly, a total of 10,038 participants aged 40 to 69 were recruited from two population-based cohorts comprising the rural Ansung (n=5,018) and urban Ansan (n=5,020) cohorts. The two cohorts were established as part of the Korean Genome Epidemiology Study (KoGES). All samples were genotyped with Affymetrix Genome-Wide Human SNP array 5.0. HbA1c was analyzed centrally with high performance liquid chromatography (Variant II, BioRad, Hercules, CA), and the values were converted to the diabetes control and complications trial (DCCT) aligned reference HbA_{1C} [3].

National Center for Global health and Medicine hospital-based cohort study (CAGE-NCGM) aims to prospectively investigate the relationship between genetic and non-genetic factors. The participants were enrolled for the detailed examination of lifestyle and lifestyle-related diseases such as cardiovascular diseases, cancer, and diabetes mellitus. It constitutes a sub-cohort of the study group of the CArdiovascular Genomic Epidemiology (CAGE) Network [4]. Non-diabetic subjects were chosen from the clinical practice or the annual medical checkup of the NCGM hospital. The inclusion criteria were as follows: 1) no past history of urinary glucose or glucose intolerance; 2) HbA_{1C}, <5.6% or a normal glucose (75g) tolerance test; and 3) age at examination, ≥55 years. Blood samples were drawn after an overnight fast to measure fasting plasma glucose (FPG) and HbA_{1C} when applicable. FPG concentrations were measured by the glucose electrode method. HbA_{1C} levels were measured by high-pressure liquid chromatography (HPLC), for which the routine measurement of HbA_{1C} was standardized using a reference material, Lot2, certified by the Japan Diabetes Society.

The Nutrition and Health of Aging Population in China (NHAPC) is a population-based cohort study among 3,289 individuals (3,210 of them are Chinese Hans), aged 50 to 70 years, recruited from Beijing and Shanghai. The study design, methods and measurements of this cohort study have been described in detail elsewhere [5]. Briefly, the participants were recruited using a multistage sampling method from 2 urban districts and 1 rural district of each city. Data on demographic variables, health status, health behavior, and physical activity was collected using a standardized questionnaire. Standard anthropometric measurements and overnight fasting blood samples were collected using a standardized protocol when the participants attended a physical examination. The DNA samples were genotyped using the Illumina Human660W-Quad BeadChip (Illumina, Inc., San Diego, CA, USA). In total,

2,507 samples with genotypes, HbA_{1C} measurements, and covariate information were included in this analysis.

Singapore Malay Eye Study (SiMES) aims to investigate the epidemiology of eye diseases and traits in Singaporean Malay. The study adopted a population-based, cross-sectional design. 3,280 Malay adults living in 15 residential districts in the southwestern part of Singapore were recruited [6]. All participants had 40 ml non-fasting venous blood drawn and collected in plain and fluoride oxalate tubes and stored at 4°C for a maximum of 4 h prior to processing. HbA_{1C}, among other things, was measured at the National University Hospital Reference Laboratory, which is accredited by the College of American Pathologists. The HbA_{1C} assay was carried out using an HPLC cation exchange chromatography system implemented on a Bio-Rad variant II analyser (Bio-Rad Laboratories, Hercules, CA, USA). The assay was accredited by the National Glycoprotein Standardization Program with controls traceable to the DCCT [7]. The DNA samples of 3,242 participants were genotyped using Illumina HumanHap 610 Quad SNP array. The first 2 PCs were included as covariates in addition to the sex and BMI in the association tests.

Singapore Chinese Eye Study (SCES) is the Chinese equivalent to SiMES, where the sampling was similarly performed in the same 15 residential districts and included 3,353 Chinese [8]. Non-fasting blood sample collection and HbA_{1C} measurement were done in the same as in SiMES [7]. The DNA samples of 1,949 participants were genotyped using the Illumina HumanHap 610 Quad SNP array.

Singapore Prospective Study Program (SP2) comprised participants of the ages between 24 and 95 years from four previous cross-sectional studies: Thyroid and Heart Study (1982–1984) [9], National Health Survey (1992) [10], National University of Singapore Heart Study (1993–1995) [11] and the National Health Survey (1998) [12]. Each of these studies sampled individuals randomly from the Singapore population. A disproportionate sampling scheme was utilized to increase the sample sizes of the minority ethnic groups (Malays and Asian Indians). Between 2003 and 2007, 10,747 participants were invited to participate in a follow up study, of which 5,157 people completed the questionnaire and the subsequent clinical examination [13]. Only Chinese individuals were included in this study. The whole batch of 3,236 samples of which fasting blood samples have been taken, were divided into three cohorts as per the genotyping platform used, which are SP2-1M (genotyped by Illumina HumanHap 1Mduo), SP2-610 (610Quad) and SP2-550 (550K). HbA_{1C} was measured using a HaemoCue Glucose Analyser (Ängelholm, Sweden).

Taiwan Super Control Study (TWSC) included 1000 randomly selected individuals, of which genetic data were extracted from the Han-Chinese Cell and Genome Bank in Taiwan [14]. In this Biobank, more than 3300 healthy controls were recruited via a stratified, 3-staged probability clustering sampling scheme through the registry of all the 329 non-aboriginal townships or city districts in Taiwan [15]. Their genomic DNA was extracted from peripheral blood using the Puregene DNA isolation kit (Gentra Systems, Minneapolis, MN, USA).

The **Singapore Chinese Health Study (SCHS)** is a cohort study of 63,257 Singaporean Chinese men and women of the Hokkien or Cantonese dialect group aged 45-74 years and residing in public housing estates (where 86% of Singaporeans live) [16]. The recruitment and the assessment of baseline diet and other characteristics through in-person interviews in the participants' home took place from 1993 to 1998 (response rate 85%). A follow-up telephone interview took place between 1999 and 2004 for 52,325 cohort members (83% of recruited cohort). By April 2005, all surviving cohort subjects had been contacted for biospecimen donation. Samples were obtained from 32,535 subjects, representing a consent rate of about 60%. The institutional review boards at the National University of Singapore, the University of Minnesota, and the University of Pittsburgh approved this study. Non-fasting venous blood was collected in 28,439 participants between 2000 and 2005. The cohort has been followed up

for mortality and morbidity through regular record linkage with the Singapore Cancer Registry, the Hospital Discharge Summary Database and the Singapore Registry of Births and Deaths through collaboration with the Ministry of Health. Percentage of HbA1c was analyzed in a Clinical Laboratory Improvement Amendments-certified laboratory using an automated high-performance liquid chromatography method where whole blood samples are treated with ethylenediaminetetraacetic acid on a Tosoh G7 HPLC Glycohemoglobin Analyzer (Tosoh Medics, Inc., San Francisco, California). Using the standards developed in the National Glycohemoglobin Standardization Program, this method of percentage of HbA1c assessment was calibrated to the reference range of 4.3%-6.0% (23 - 42 mmol/mol) and the laboratory coefficient of variation range was 1.4%-1.9%.

Two case-control sub cohorts were drawn from SCHS. They are SCHS Diabetes (SCHS-DB) and SCHS Coronary Heart Disease (SCHS-CHD), aiming to study the genetic and environmental risk factors of diabetes mellitus and coronary heart disease, respectively. For SCHS-DB, we excluded subjects with prevalent diabetes, cardiovascular disease, or cancer at the baseline interview, and those without stored tissue samples. 24,932 subjects remained. Among them, we identified 2,615 incident diabetes cases and 2,615 controls matched on age, gender, dialect group (Cantonese or Hokkien), and date of blood draw. A total of 4,677 samples (2338 cases and 2339 controls) remained after SNP array data QC. 2,009 controls with complete HbA_{1C} < 6.0% and covariate information were included in this study. For SCHS-CHD, cases had fatal coronary heart disease or non-fatal myocardial infarction (MI) identified through the Singapore Registry of Births and Deaths and the Hospital Discharge Database respectively. For all non-fatal cases, medical records were retrieved for review by a cardiologist and we only included those that have confirmed myocardial infarction using the criteria of the Multi-Ethnic Study of Atherosclerosis. Cases of fatal CHD were only included if there was prior evidence of CHD based on the questionnaire data or the Hospital Discharge Database. We selected cases and matched controls using the risk-set sampling strategy. Controls were participants who were alive and free of coronary heart disease at the time of the diagnosis or death of the index cases and matched (1 to 2) for sex, dialect group, year of birth, year of recruitment and date of blood collection. Genotyping was performed for 2,136 SCHS samples using the Illumina OmniZhonghua array. After SNP array data QC, 1,024 controls and 457 cases remained with complete HbA_{1C} and covariate information. Both cases and controls were included in this study, while the association analysis was done in cases and controls separately.

Shanghai Breast Cancer Study (SBCS) included two recruitment phases, as described in detail elsewhere [17,18]. 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 in SBCS-I. 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. Current study only included controls who have both HbA_{1C} profile data and GWAS data.

Stage 2 cohorts

The **TaiChi** consortium was formed through a collaborative effort between investigators based in the U.S. and Taiwan. The consortium's primary aim is to identify genetic determinants of atherosclerosis and diabetes related traits in Han Chinese and to fine-map validated loci identified in other race/ethnic groups [19]. The main academic sites participating in the TaiChi consortium in Taiwan include Taichung Veteran's General Hospitals, Taipei Veterans General Hospital, National Health Research Institutes, Tri-Service General Hospital, and National Taiwan University Hospital. The main U.S. academic sites include Stanford University School of Medicine in Stanford, California; Hudson-Alpha Biotechnology

Institute in Huntsville, Alabama; Los Angeles BioMedical Research Institute at Harbor-UCLA Medical Center in Torrance, California; and Cedars-Sinai Medical Center (CSMC) in Los Angeles, California. TaiChi brings together 7 principal cohorts formed in Taiwan producing a bio-resource that includes a total of 11,859 subjects. For the current study, 1,984 of these subjects had HbA_{1C} data and met inclusion criteria. PC1 was included in addition to sex and BMI in the association test. HbA_{1C} was measured by HPLC, D-10 Hemoglobin A_{1C} program, Bio RAD by Union Clinical Laboratory in 95% of the samples.

The Kyushu University Fukuoka Cohort Study (CAGE-Fukuoka) is a community-based prospective epidemiologic cohort of 12,959 subjects, who participated in the baseline survey during the period from February 2004 to August 2007 [20]. From this cohort, 12,569 subjects completed the questionnaire and also provided DNA for genotyping of SNPs to investigate lifestyle factors and genetic susceptibility of the so-called lifestyle-related diseases such as cardiovascular diseases, cancer, and diabetes mellitus. Since blood was not drawn strictly after an overnight fast, HbA_{1c} was measured in all participants from the Kyushu University Fukuoka Cohort Study to evaluate impaired glucose metabolism. From the participants, 4,889 individuals were chosen as non-diabetic participants who met the following conditions: age ≥55 years; HbA_{1c} ≤5.0%; no previous and/or current treatment for diabetes; and absence of renal failure (serum creatinine < 265.2 mmol/l). HbA_{1C} levels were measured by high-pressure liquid chromatography, as described in the section of NCGM Hospital-based Cohort Study.

The Japanese Millenium Genome Project (JMGP) comprises 8 independent study cohorts for studies of cardiovascular diseases and related risk factors. Among them, three cohorts of general Japanese population, namely AAC, Shigaraki, and Takashima were included in this analysis [21]. The AAC cohort subjects were consecutive participants of the medical check-up program at Ehime University Hospital anti-aging center. This check-up program is specifically designed to evaluate aging-related disorders, including atherosclerosis, cardiovascular disease, physical function and mild cognitive impairment. All clinical data used in this study were obtained through the check-up process. The Takashima study is an ongoing longitudinal study based on a community of residents living in Takashima City. Takashima City is an urban area located in Shiga prefecture with a population of approximately 54,000. Study subjects were recruited between 2002 and 2003 from participants in the annual medical check-up program performed by Takashima City office. The basic clinical parameters used in this study were obtained from the personal medical check-up records of the subjects. The Shigaraki study is another longitudinal study based on community residents in Shigaraki-town, a farming community located in Shiga prefecture. The Shigaraki study was based on a medical examination undertaken by Shigaraki-town Office in 1999. The basic clinical parameters used in this study were also obtained from the personal medical check-up records.

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SUPPLEMENTARY DATA

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Age, Gene/Environment Susceptibility-Reykjavik Study (AGES)

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CHARGE Hematology Working Group

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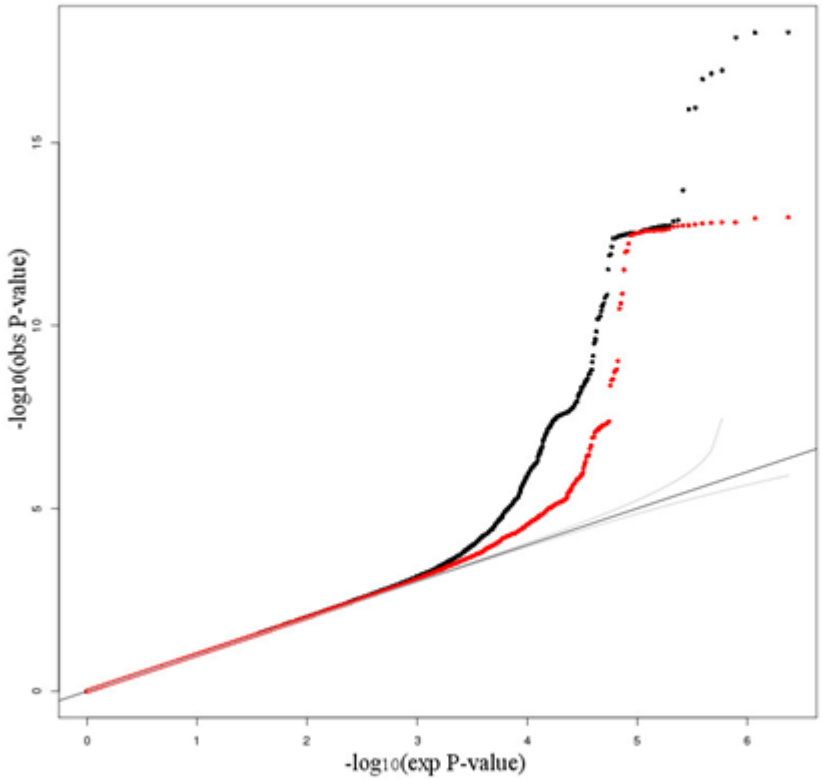
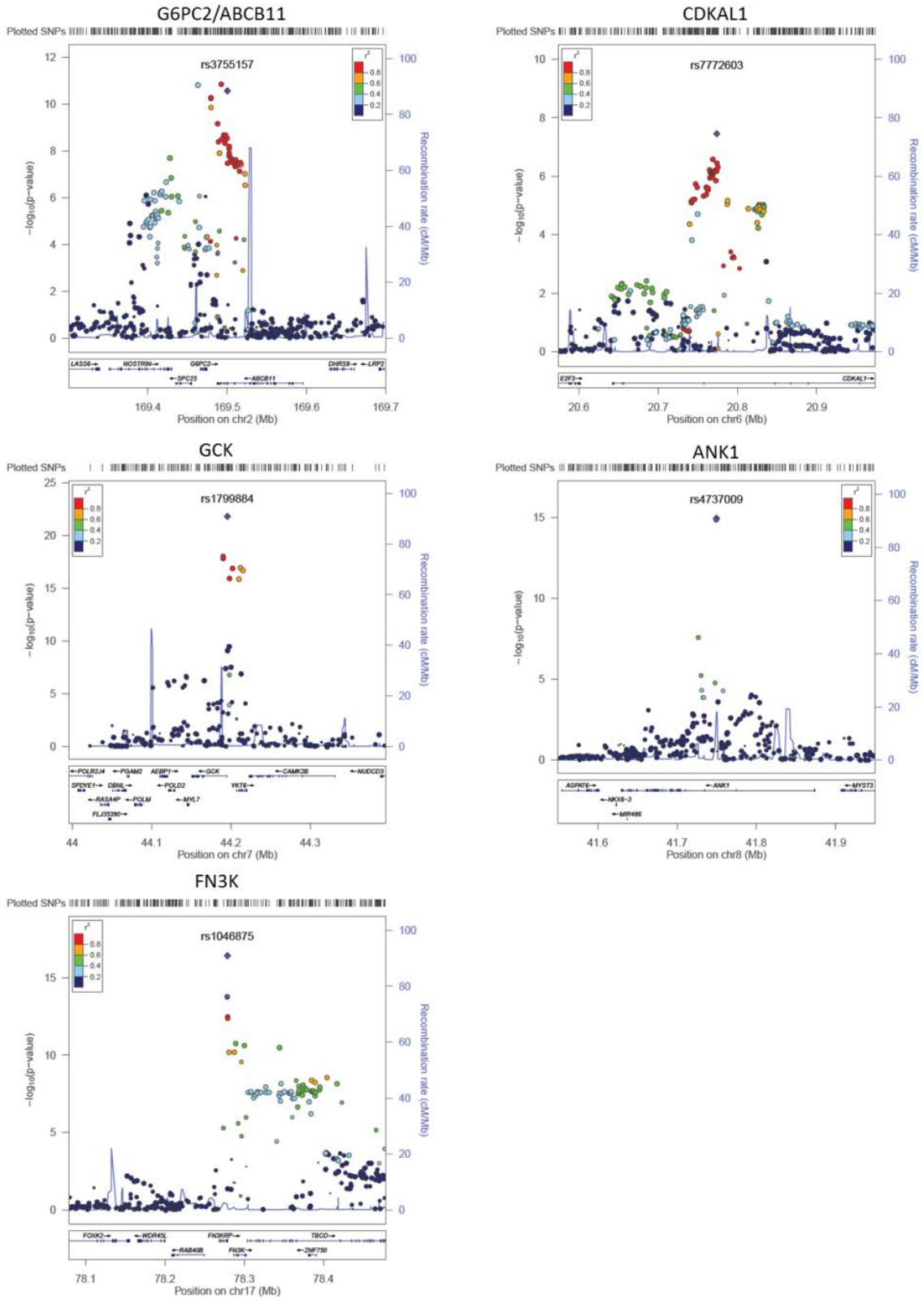
SUPPLEMENTARY DATA

Supplementary Figure 1. Q-Q plot of the Stage 1 meta-analysis with/without known SNPs. The expected P values (X-axis) are plotted against the observed P-values (Y-axis). The units of the axes are the $-\log_{10}$ of the P-value. The black and red curves represent the plots with and without the SNPs in LD ($r^2 > 0.2$) with known SNPs associated with HbA_{1C} respectively. The diagonal line of the null hypothesis and its 95% confidence interval were plotted in grey based on the P-values without the previously reported SNPs.



SUPPLEMENTARY DATA

Supplementary Figure 2. Regional association plot of the known loci. P-values are plotted against the genomic coordinates. The index SNPs are indicated in purple, with circles for Stage 1 and diamonds for Stage 1+2. Other SNPs are colored from red to blue as per their LD with the index SNP.



SUPPLEMENTARY DATA

Supplementary Table 1. Genotyping, QC, imputation and association testing in each study.

		Sample QC					SNP QC			Imputation		Association Testing	Exclusion	
Study Name	Genotyping	Call rate	Cryptic realtionship	Population outlier	Hetero-zygosity	Gender consistency	Call rate	HWE P value	MAF	Reference Panel (HapMap Phase 2)	Imputation software	Association Software	FG > 7 mmol/L?	HbA1C >6.5%?
Stage 1														
CRC	Illu 660Quad	95%	Yes	Yes	Yes	Yes	98%	1E-6	1%	R22 JPT+CHB	MACH 1.0	Plink v1.07	Yes	no
KARE	Affy 5.0	98%	yes	yes	yes	yes	95%	1E-6	1%	r22 JPT+CHB	IMPUTE V1.0	Plink v1.07	Yes	No
CAGE-NCGM	Illu 550	90%	yes	yes	yes	yes	95%	1E-6	1%	r24 JPT+CHB	BEAGLE v3.0.4	PLINK v1.06	Yes	Yes
NHAPC	Illu 660W	97%	yes	yes	yes	yes	99%	1E-6	1%	r22 JPT+CHB	IMPUTE v2.1	SNPTEST v2.2.0	yes	no
SCES	Illu 610Quad	95%	yes	yes	yes	yes	95%	1E-6	none	r22 JPT+CHB	IMPUTE v2.2	SNPTEST v2.4.1	No	Yes
SiMES	Illu 610Quad	95%	yes	yes	yes	yes	95%	1E-6	none	r22 JPT+CHB+CEU+YRI	IMPUTE v0.5	SNPTEST v2.4.1	No	Yes
SP2-610	Illu 610Quad	95%	yes	yes	yes	yes	95%	1E-6	none	r22 JPT+CHB	IMPUTE v0.5	SNPTEST v2.4.1	Yes	Yes
SP2-1M	Illu 1MDuo	95%	yes	yes	yes	yes	95%	1E-6	none	r22 JPT+CHB	IMPUTE v0.5	SNPTEST v2.4.1	Yes	Yes
SP2-550	Illu 550 v3	95%	yes	yes	yes	yes	95%	1E-6	none	r22 JPT+CHB	IMPUTE v0.5	SNPTEST v2.4.1	Yes	Yes
TWSC	Illu 550Duo	95%	yes	yes	yes	yes	95%	1E-4	1%	r22 JPT+CHB	MACH 1.0	PLINK v1.07	No	Yes
SCHS-CHD	Illu Omni Zhonghua8	98%	yes	yes	yes	yes	95%	1E-5	1%	r22 JPT+CHB	IMPUTE v2	SNPTEST v2.4.1	No	YES
SBCS	Affy 6.0	95%	yes	yes	yes	yes	95%	1E-6	1%	r22 JPT+CHB	MACH 1.0	mach2qtl	Yes	Yes
SCHS-DB	Affy Axiom	98%	yes	yes	yes	yes	99%	1E-4	none	r22 JPT+CHB	IMPUTE v2	SAS 9.2		
Stage 2														
TaiChi	Illu Cardio-Metabochip	98%	yes	yes	yes	yes	97%	1E-7	1%	NA	NA	Plink	yes	yes
CAGE-Fukuoka	TaqMan	no	no	no	no	no	no	1E-4	none	NA	NA	R v2.14.1	No	Yes
JMGP	TaqMan	no	no	no	no	no	no	no	no	NA	NA		Yes	No

SUPPLEMENTARY DATA

Supplementary Table 2. Heterogeneity test of the effects in the recruited cohorts.

SNP	Gene	HetISq	HetPVal
rs540078	PSMD13	39.6	0.052
rs9933309	CYBA	0.0	0.539
rs11667918	MYO9B	32.3	0.104
rs6684514	TMEM79	0.0	0.709
rs174570	FADS2	25.0	0.166
rs1467311	9q31.2	26.5	0.151
rs9399137	HBS1L/MYB	12.3	0.313
rs1046875	FN3K	37.0	0.074
rs13266634	SLC30A8	10.2	0.341
rs1799884	GCK	0.0	0.678
rs3755157	G6PC2/ABCB11	43.3	0.043
rs4737009	ANK1	8.3	0.361
rs7772603	CDKAL1	0.0	0.581

HetISq is the I2 statistics of heterogeneity;
HetPVal is the P-value for heterogeneity.

SUPPLEMENTARY DATA

Supplementary Table 3. LD between index SNPs identified in this study and index SNPs identified previously at the known loci. The degree of linkage disequilibrium (r^2) is provided for HapMap CEU and JPT+CHB panels separately. The minor allele frequency (MAF) of the index SNP is presented in HapMap CEU / JPT+CHB panels, where MAF (EA) represents the MAF of the East Asian index SNP and MAF (Reported) represents the index SNP in the published GWAS. The references are also given for each reported index SNP. Soranzo *et. al.* refers to Supplementary Reference [22]; Pare et. al. refers to Supplementary Reference [23]; Ryu et. al. refers to Supplementary Reference [24]; Franklin et. al. refers to Supplementary Reference [25]. Reported ancestry refers to the population ancestry in which the association of the reported index SNP was discovered for the first time.

	East Asian	Reported		r^2					Reported
Gene	Index SNP	Index SNP	Distance	CEU	JPT+CHB	MAF (EA)	MAF (Reported)	reference	Ancestry
G6PC2/ABCB11	rs3755157	rs552976	733	**0.05**	**0.00**	0.09/0.39	0.35/0.01	Soranzo et.al	European
GCK	rs1799884	rs1799884	0	1.00	1.00	0.20/0.19	0.20/0.19	Soranzo et.al	European
		rs730497	5,347	1.00	1.00	0.20/0.19	0.20/0.19	Pare et.al	European
ANK1	rs4737009	rs4737009	0	1.00	1.00	0.28/0.46	0.28/0.46	Soranzo et.al	European
		rs6474359	81,211	**0.00**	**0.01**	0.28/0.46	0.03/0.07	Soranzo et.al	European
FN3K	rs1046875	rs1046896	107	1.00	1.00	0.25/0.47	0.25/0.47	Soranzo et.al	European
CDKAL1	rs7772603	rs7747752	59,477	**0.17**	0.61	0.31/0.39	0.21/0.46	Ryu et.al	Korean

SUPPLEMENTARY DATA

Supplementary Table 4. The association of the index SNPs reaching genome-wide significance in association with HbA_{1c} in our study with T2D, fasting glucose and 2hr oral glucose challenge test. The Stage 1 index SNPs were looked up in DIAGRAM T2D study [26] and MAGIC fasting glucose and 2HR oral glucose challenge study [27,28], AGEN T2D study [29], and a Korean fasting glucose study [30]. Statistical significance was defined after Bonferroni correction at P-value < $0.05/9/5 \approx 1.1 \times 10^{-3}$. The statistically significant loci are highlighted in bold.

SNP	rs6684514	rs3755157	rs7772603	rs9399137	rs1799884	rs4737009	rs9933309	rs1046875	rs11667918
Gene	TMEM79	G6PC2/ABCB11	CDKAL1	HBS1L/MYB	GCK	ANK1	CYBA	FN3K	MYO9B
MAGIC FG	2.2E-02	**1.9E-09**	1.3E-02	1.3E-03	**6.4E-37**	2.7E-01	6.0E-01	3.0E-01	1.1E-01
MAGIC 2HR	5.9E-01	6.9E-01	1.4E-01	4.3E-01	**2.7E-04**	9.4E-01	6.4E-01	4.9E-01	9.2E-02
AGEN T2D	1.9E-02	4.0E-01	**6.3E-15**	3.3E-01	4.6E-01	3.0E-01	9.2E-01	3.0E-01	6.6E-01
AGEN FG	1.2E-01	**5.2E-31**	**2.1E-07**	9.3E-01	**3.6E-27**	3.3E-01	2.3E-01	4.4E-01	7.3E-01
Diagram T2D	6.5E-01	8.3E-02	**1.3E-15**	1.3E-01	4.2E-02	1.4E-01	6.2E-01	6.9E-01	7.3E-01

Supplementary Table 5. The effects of the association with T2D, fasting glucose and 2hr oral glucose challenge test of the HbA_{1C} index SNPs.

SNP	rs6684514	rs3755157	rs7772603	rs9399137	rs1799884	rs4737009	rs9933309	rs1046875	rs11667918
Gene	TMEM79	G6PC2/ABCB11	CDKAL1	HBS1L/MYB	GCK	ANK1	CYBA	FN3K	MYO9B
Alleles	G/A	C/T	C/T	C/T	T/C	A/G	T/C	A/G	C/T
MAGIC FG	0.009	**-0.035**	0.010	-0.013	**0.062**	0.005	-0.003	0.004	0.007
MAGIC 2HR	0.011	-0.011	0.030	-0.017	**0.096**	-0.002	0.015	0.016	0.036
AGEN T2D	0.940	1.021	**1.210**	0.975	1.022	0.971	0.997	1.024	1.013
AGEN FG	0.016	**-0.107**	**0.050**	-0.001	**0.122**	0.009	0.015	0.007	-0.003
Diagram T2D	1.010	1.050	**1.170**	1.030	1.050	1.030	1.010	1.010	1.010

The effects in bold are those significant as showed in Supplementary Table S4. For the T2D associations, the effects are given as odds ratio, while others are the beta coefficients.

SUPPLEMENTARY DATA

Supplementary Table 6. Comparison of the allele frequency, effect size and P-value for known variants associated with HbA_{1C} between the previous study and this study. The previous reports include Soranzo et. al. [22], Pare et. al. [23], Ryu et. al [24] and Franklin et. al. [25]. The effect allele frequencies are from HapMap phase 2 release 22 CEU and JPT+CHB panels, depending on the ancestry of the study. The effect allele, effect and P-value information of Soranzo *et. al.* were downloaded from http://www.magicinvestigators.org/.

			AGEN			Previous GWAS				
SNP	Gene	Effect_Allele	P	Effect	Freq	P	Effect	Freq	Ancestry	First
rs4737009	ANK1	A	7.6E-15	0.09	0.46	6.0E-12	0.03	0.28	European	Soranzo
rs6474359	ANK1	T	8.2E-03	-0.08	0.07	1.0E-08	0.06	0.03	European	Soranzo
rs7998202	ATP11A /TUBGCP3	G	1.2E-02	0.07	0.09	5.0E-09	0.03	0.17	European	Soranzo
rs7747752	CDKAL1	C	8.0E-06	0.05	0.46	1.0E-11	0.01	0.21	Asian	Ryu
rs1046896	FN3K	T	1.4E-13	0.07	0.47	2.0E-26	0.03	0.25	European	Soranzo
rs1402837	G6PC2 /ABCB11	A	5.8E-07	0.07	0.47	5.0E-10	0.03	0.30	European	Pare
rs552976	G6PC2 /ABCB11	G	5.3E-01	0.03	0.01	8.0E-18	0.03	0.35	European	Soranzo
rs1799884	GCK	T	2.7E-19	0.12	0.19	1.0E-20	0.04	0.20	European	Soranzo
rs730497	GCK	A	3.7E-19	0.12	0.19	6.0E-12	0.04	0.20	European	Pare
rs1800562	HFE	G	NA	NA	0.00	3.0E-20	0.06	0.04	European	Soranzo
rs16926246	HK1	C	NA	NA	0.02	3.0E-54	0.09	0.11	European	Soranzo
rs7072268	HK1	A	8.4E-02	0.02	0.28	2.0E-25	0.02	0.44	European	Pare
rs1387153	MTNR1B	T	2.8E-02	0.03	0.50	4.0E-11	0.03	0.28	European	Soranzo
rs13266634	SLC30A8	A	1.5E-07	-0.05	0.46	5.0E-08	-0.02	0.30	European	Pare
rs2779116	SPTA1	T	1.0E-04	0.04	0.38	3.0E-09	0.02	0.32	European	Soranzo
rs7903146	TCF7L2	C	5.8E-01	-0.02	0.02	1.0E-07	-0.01	0.25	European	Franklin
rs855791	TMPRSS6	A	1.3E-04	0.05	0.45	3.0E-14	0.03	0.39	European	Soranzo

Supplementary Table 7. Comparison of the allele frequency, effect size and P-value for novel variants identified in this study compared to those observed in the populations of European ancestry [22]. The effect allele frequencies are from HapMap phase 2 release 22 JPT+CHB and CEU panels, respectively.

			AGEN			MAGIC		
SNP	Gene	Effect_Allele	P	Effect	Freq	P	Effect	Freq
rs1467311	9q31.2	G	1.0E-06	0.04	0.24	9.4E-03	0.01	0.29
rs9933309	CYBA	C	1.1E-08	0.07	0.38	1.2E-04	0.02	0.29
rs174570	FADS2	C	2.0E-07	0.04	0.33	8.5E-02	0.01	0.16
rs9399137	HBS1L/MYB	T	8.5E-15	0.07	0.32	8.1E-05	0.02	0.23
rs11667918	MYO9B	C	9.0E-12	0.06	0.39	3.7E-05	0.02	0.24
rs540078	PSMD13	T	3.2E-05	0.03	0.40	1.3E-01	0.02	0.06
rs6684514	TMEM79	G	1.3E-23	0.09	0.22	4.0E-02	-0.01	0.27

SUPPLEMENTARY DATA

Supplementary Table 8. The association of the HbA_{1C} index SNPs with hemoglobin related traits. The associations were looked up from three large consortia meta-analysis, Kamatani et. al. [31], Soranzo et. al. [32] and Ganesh et. al. [33]. Hb, hemoglobin concentration; HCT, hematocrit; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; RBC, red blood cell count; PCV, packed cell volumn. Statistical significance was defined after Bonferoni correction at $p < 0.05/17/9 = 3.3 \times 10^{-4}$. Significant P-values were highlighted in bold.

SNP		rs6684514	rs3755157	rs7772603	rs9399137	rs1799884	rs4737009	rs9933309	rs1046875	rs11667918
Gene		TMEM79	G6PC2/ABCB11	CDKAL1	HBS1L/MYB	GCK	ANK1	CYBA	FN3K	MYO9B
Hb	RIKEN	6.5E-02	5.3E-01	7.6E-01	**2.8E-04**	6.5E-01	7.5E-01	5.7E-02	6.5E-01	3.2E-01
	HaemGen	1.9E-01	8.4E-01	2.1E-01	**8.5E-08**	3.6E-01	2.4E-03	**2.6E-05**	3.8E-01	4.7E-01
	CHARGE	2.4E-01	3.7E-01	9.6E-01	**1.6E-10**	3.6E-01	4.4E-01	2.7E-02	8.7E-01	1.1E-01
HCT	RIKEN	7.4E-01	6.5E-01	8.1E-01	**2.6E-09**	9.9E-01	2.2E-01	9.4E-01	7.3E-01	1.3E-01
	CHARGE	2.4E-01	3.7E-01	9.6E-01	**1.6E-10**	3.6E-01	4.4E-01	2.7E-02	8.7E-01	1.1E-01
MCH	RIKEN	2.4E-01	5.4E-01	1.7E-01	**2.1E-54**	5.3E-01	5.7E-01	4.4E-01	2.3E-01	9.7E-01
	HaemGen	1.3E-01	9.6E-01	9.2E-01	**4.8E-91**	4.5E-01	2.9E-01	1.1E-01	1.5E-01	3.4E-02
	CHARGE	5.6E-01	5.8E-01	6.1E-01	**2.0E-33**	9.6E-01	7.4E-02	5.4E-01	2.3E-02	6.9E-01
MCHC	RIKEN	**3.5E-08**	6.1E-01	3.9E-01	**6.1E-09**	3.6E-01	3.7E-04	**1.2E-09**	6.0E-01	1.4E-01
	HaemGen	9.6E-01	6.1E-01	9.6E-01	**5.0E-06**	1.7E-01	**4.9E-05**	2.7E-03	1.7E-01	3.0E-01
	CHARGE	4.2E-01	8.9E-01	6.3E-01	**1.7E-09**	8.0E-01	**4.6E-05**	1.0E-01	7.8E-01	1.6E-01
MCV	RIKEN	**1.5E-04**	5.3E-01	3.1E-01	**2.6E-45**	6.6E-01	3.0E-02	**5.9E-05**	1.9E-01	6.7E-01
	HaemGen	1.9E-02	3.5E-01	4.2E-01	**1.2E-88**	1.8E-01	**3.6E-06**	8.6E-02	3.7E-01	2.0E-03
	CHARGE	6.3E-01	5.4E-01	4.5E-01	**6.9E-57**	9.2E-01	**1.2E-04**	8.4E-01	5.4E-03	4.3E-01
RBC	RIKEN	2.6E-02	5.7E-01	7.5E-01	**4.2E-40**	6.8E-01	8.4E-01	8.4E-02	1.0E+00	1.7E-01
	CHARGE	6.5E-01	2.6E-01	1.7E-01	**1.0E-18**	7.4E-01	2.8E-01	6.8E-02	1.0E+00	5.6E-01
PCV	HaemGen	3.6E-01	7.4E-01	4.9E-01	**1.2E-17**	9.1E-01	2.7E-01	3.0E-01	8.2E-02	9.5E-01

SUPPLEMENTARY DATA

Supplementary Table 9. The effects of the association with hemoglobin related traits of the HbA_{1C} index SNPs.

SNP		rs6684514	rs3755157	rs7772603	rs9399137	rs1799884	rs4737009	rs9933309	rs1046875	rs11667918
Gene		TMEM79	G6PC2/ABCB11	CDKAL1	HBS1L/MYB	GCK	ANK1	CYBA	FN3K	MYO9B
Alleles		G/A	C/T	C/T	C/T	T/C	A/G	T/C	A/G	C/T
Hb	RIKEN	0.033	0.009	-0.005	**-0.055**	0.009	0.006	0.028	0.007	0.016
	HaemGen	0.009	-0.002	0.008	**-0.035**	0.008	-0.023	**0.029**	-0.006	-0.006
	CHARGE	-0.038	-0.040	0.001	**-0.198**	0.033	0.025	0.076	-0.005	0.049
HCT	RIKEN	0.017	0.019	-0.010	**-0.256**	0.000	0.067	0.003	0.015	0.069
	CHARGE	-0.038	-0.040	0.001	**-0.198**	0.033	0.025	0.076	-0.005	0.049
MCH	RIKEN	-0.001	0.000	-0.001	**0.011**	0.001	0.001	-0.001	0.001	0.000
	HaemGen	0.018	-0.001	0.001	**0.239**	-0.011	0.014	0.021	0.017	0.029
	CHARGE	-0.001	0.001	0.000	**0.009**	0.000	0.002	0.001	-0.003	0.000
MCHC	RIKEN	**0.002**	0.000	0.000	**0.002**	0.000	-0.001	**0.002**	0.000	0.000
	HaemGen	0.000	0.003	0.000	**0.019**	-0.006	**-0.018**	0.013	0.006	-0.005
	CHARGE	0.000	0.000	0.000	**0.002**	0.000	**-0.002**	0.001	0.000	-0.001
MCV	RIKEN	**-0.003**	0.000	-0.001	**0.009**	0.000	0.002	**-0.002**	0.001	0.000
	HaemGen	0.071	-0.039	-0.023	**0.601**	-0.050	**0.156**	-0.057	0.027	0.111
	CHARGE	0.000	0.001	0.000	**0.008**	0.000	**0.002**	0.000	-0.002	0.000
RBC	RIKEN	0.003	0.001	0.000	**-0.016**	-0.001	0.000	0.002	0.000	0.002
	CHARGE	-0.001	-0.003	0.002	**-0.013**	0.001	-0.002	0.004	0.000	-0.001
PCV	HaemGen	0.019	0.010	0.013	**-0.175**	-0.003	-0.026	0.023	-0.037	0.002

The effects in bold are those significant as showed in Supplementary Table S8. All the effects are beta coefficients

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