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Subjects

The GWA study for T2D was performed with a three-stage design using the following Japanese samples. All study subjects were unrelated, and they provided written consent for participation. All methods of the study were approved by the ethics committees at the International Medical Center of Japan and the individual institutions involved in the present study.
1) Stage-1 and stage-2 samples
Cases and unaffected controls analyzed in stages 1 and 2 were enrolled according to the identical criteria and their baseline characteristics are shown in Supplementary Table S1. T2D cases were enrolled from the clinical practice or the annual medical checkup of university hospitals, medical institutions, and general practitioners that constitute the Study Group of the NIBIO GWA (the list of which is shown in acknowledgment) according to the 1999 WHO criteria [Geneva, World Health Organization (1999)]. Exclusion criteria for cases were individuals with diabetes due to: [1] liver dysfunction; [2] monogenic disorder known to cause diabetes; and [3] positive anti-GAD antibody. The inclusion criteria for controls were as follows: [1] no past history of urinary glucose or glucose intolerance; [2] HbA1c, <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 blood glucose and HbA1c when applicable.

2) Stage-3 samples
Stage-3 samples comprised 4,000 T2D cases derived from the Biobank Japan project and a total of 12,569 subjects randomly selected from residents aged 50–74 years in the general population. From this population-based cohort, 4,889 controls were chosen for the genotype comparison with 4,000 T2D cases.

2-1. Biobank Japan samples
The BioBank Japan project (Reference 27; http://biobankjp.org/) was begun in 2003 for the collection of genomic DNA, serum, and clinical information from a total of >280,000 cases diagnosed with either of 47 diseases by a collaboration network of 66 hospitals in Japan. Patients gave written informed consent to participate in this project before information was collected. From the registered samples in the BioBank Japan, we selected 4,000 patients who were diagnosed as T2D.
2-2. *Samples from general population cohort*

The study subjects were participants in the baseline survey of the Kyushu University Fukuoka Cohort Study, which was designed to investigate lifestyle factors and genetic susceptibility of the so-called lifestyle-related diseases such as cardiovascular diseases, cancer, and diabetes mellitus. Eligible persons were residents of the East Ward of Fukuoka City aged 50 to 74 years. Some areas in the Ward were excluded because of potential emigration, sparse population, and remote distance. Of 53,927 persons who were contacted by mail, a total of 12,959 participated in the baseline survey during the period from February 2004 to August 2007. Brief description of the methods in the baseline survey is available elsewhere (51).

Excluding 8 for withdrawal, one for duplicate participation, and one for mental incompetence, the cohort comprised 12,949 persons. Of them, 12,629 gave informed consent to genetic analysis. For DNA extraction, 6 ml of venous blood was drawn into a vacuum tube containing EDTA-K2. Within at most 8 hours of blood sampling, 2 ml of plasma was taken after centrifugation, and the remaining blood sample added with 1 ml PBS was stored at –80 °C until DNA extraction. DNA was extracted from the peripheral leukocyte fraction using automatic nucleic acid isolation system NA-3000 (Kurabo, Tokyo, Japan) and stored at –80 °C until genotyping. A total of 12,569 subjects completed the questionnaire and also provided DNA for genotyping of SNPs.

As non-diabetic controls from the general population, we arbitrarily selected 4,889 subjects (2,259 men and 2,630 women) who met the following conditions: age, ≥55 years; HbA1c, ≤ 5.0%; no previous and/or current treatment for diabetes; and absence of renal failure (serum creatinine, <3.0 mg/dl).

The outline of the stage-3 analysis is shown in Figure 1. As for the SNPs detected by GWA scans (17 SNPs), which surpassed the stage-2 threshold and were taken forward in stage 3, 4,000 T2D cases (from the BioBank Japan project) and 4,889 controls were characterized for replication. On the other hand, as for the
previously-reported SNPs (6 SNPs apart from rs7754840 and rs7756992 in CDKAL1 and rs10811661 in CDKN2A/2B), which were replicated in the stage 1+2 panel and were taken forward in stage 3, the same (stage 3) case-control panel was first characterized, of which the confirmed SNPs (5 of the 6 SNPs tested) were further genotyped in an additional panel of 7,680 population-based samples; these subjects plus 4,889 controls constitute the entire population-based panel \((N = 12,569)\) in stage 3. Here, we took forward rs4712523 instead of rs7754840 and rs7756992 (CDKAL1), and rs2383208 instead of rs10811661 (CDKN2A/2B) in the stage-3 analysis to proceed with GWA scans from stage 1 to stage 3 by considering strong linkage disequilibrium (LD) between the SNPs in each of the corresponding loci. For the SNPs thus tested in the entire population-based panel, a total of 5,395 non-diabetic controls \((\geq 50 \text{ years and no family history of diabetes in either of parents})\) were used for the stage-3 case-control analysis and meta-analysis. That is, 506 subjects were derived from the 7,680 population-based samples additionally characterized.

Since blood was drawn not strictly on the condition of overnight fast, HbA1c was measured in all participants to evaluate the impaired glucose metabolism (52). In Japan, stable HbA1c was standardized in the mid 1990s by the Japan Diabetes Society (JDS) and has been used to estimate the number of people with probable and possible diabetes in the Japan National Diabetes Survey (JNDS) [the survey data in 2002 are available at http://www.health-net.or.jp/data/menu05/toukei/tonyo_h14.pdf (in Japanese)]. In this survey, probable diabetes was defined as HbA1c \(\geq 6.1\) or under treatment of diabetes, and possible diabetes was defined as \(5.6 \leq \text{HbA1c} < 6.1\) among those without treatment of diabetes. These cut-off points for HbA1c were chosen with respect to equivalent diagnostic cut-off points for fasting plasma glucose and 2-h plasma glucose in an oral glucose (75g) tolerance test for undiagnosed diabetes in the linear regression analysis (53). Moreover, the screening test properties of HbA1c for undiagnosed diabetes was assessed in the general population data \((N = 1,904)\) according to the 1999-WHO criteria,
which further supported the JNDS cut-off points for HbA1c with respect to screening properties of undiagnosed diabetes in Japan (54).

For the assessment of combined risk of diabetes and pre-diabetes, all the general population samples ($N = 12,569$) were used. According to the ADA [http://www.diabetes.org/pre-diabetes.jsp], pre-diabetes can be defined as the condition that blood glucose levels are higher than normal but yet high not enough to be diagnosed as diabetes. Strictly, this definition of pre-diabetes is not identical to that of possible diabetes in the JNDS, but we arbitrarily used the cut-off point of $5.6 \leq \text{HbA1c} < 6.1$ among people without treatment of diabetes as ‘pre-diabetes’ and that for probable diabetes (i.e., $\text{HbA1c} \geq 6.1$ or under treatment of diabetes) as ‘diabetes’ in our risk assessment in the general population.

Subjects with increased HbA1c levels include type 1 diabetes (T1D) as well as T2D. However, in the present study, overall, population-wide impacts of T1D seem to be negligible. Japan is known to have one of the lowest incidence rate of T1D in the world. According to population-based systems to detect childhood diabetes, the prevalence of T1D children has been estimated to be about 22.5 cases per 100,000 individuals. The prevalence of T1D in adults, on the other hand, appears more than twice that in childhood-onset patients (55), roughly indicating the T1D prevalence of $\sim 0.05\%$ in the general population. Thus, in Japan, T2D is common in diabetes mellitus in old age, and there are rarely elderly patients with T1D (56).

Stage-1 genome-wide scan and quality control

1) SNP genotyping

Genotyping was performed according to the manufacturer’s protocol by labeling 750 ng of genomic DNA and hybridizing it to the Infinium HumanHap550 BeadArray (Illumina, San Diego, CA), which interrogated 555,352 SNPs. This set of SNP markers are reported to capture 87% of common SNPs with an LD coefficient of $r^2 > 0.8$ in the
HapMap Japanese and Chinese population (according to the manufacturer’s brochure). Assay accuracy and reproducibility were measured using DNA from CEPH Utah samples (CEU) genotyped as part of the HapMap project (29). Genotype calling was performed using the BeadStudio software (Illumina), and genotype calls with the “GenTrain” score < 0.53 were dropped from analysis. The “GenTrain” score measures the reliability of genotype calls based on the clustering of dye intensities [http://www.illumina.com/downloads/ GenCallTechSpotlight.pdf]. The average call rate was 96.9% in either of cases and controls.

2) Quality control of samples
Data cleaning and analysis were done using the PLINK software (28). Samples with genotype call rate less than 90% were excluded from analysis (N = 9). We looked for outlier samples with respect to the number of heterozygous SNPs, which could be caused by poor DNA quality. We found no such outliers in the stage-1 cohort after the removal of nine samples above.

In order to detect duplicate samples, relatives, and ethnic outliers among the subjects initially tested, similarity of DNA was evaluated for each pair of samples by the proportion of identity by state (IBS) alleles over all SNPs. Sample pairs with the IBS allele proportion > 0.99 were regarded as duplicates, in which case one each from such sample pairs was removed (N = 2). For each sample, the most similar pair could typically show the IBS allele proportion of ~0.77. We found no sample pairs with a significantly larger proportion of IBS alleles, in other words, no relatives were included in the stage-1 cohort. On the contrary, any samples showing significantly less similarity to the others in the IBS allele proportion (Z-score < –5) were removed as ethnic outliers (N = 2).

For the remaining 1,022 samples, we checked ethnicity by combining them with samples from the HapMap. The HapMap individuals comprised 17 Japanese in Tokyo
(JPT), 13 Han Chinese in Beijing (CHB), 52 of CEU, and 38 Yoruba in Ibadan (YRI). Multi-dimensional scaling analysis was applied to the pairwise IBS distance between the samples. Our study samples were clearly distinctive from the non-Asian samples (CEU and YRI) and clustered identically around the JPT samples, rather than around the CHB samples (see Supplementary Figure S8). Consequently, we adopted all of the 1,022 samples (519 cases and 503 controls) for further analysis.

3) Quality control of SNPs
Among 555,352 SNPs, we excluded SNPs for which [1] genotype call rate, <0.95; [2] genotype call rate, <0.99 and minor allele frequency (MAF), <0.05; [3] significant ($P < 10^{-6}$) deviation from the Hardy-Weinberg equilibrium in the controls; or [4] MAF, < 0.001. The remaining 482,625 SNPs were analyzed in the first stage scan of GWA study (Supplementary Table S2). Representative signal intensity plots are shown in Supplementary Figure S9 for nine SNPs that emerged at the end of the three-stage scan.

Evaluation and correction of population stratification
In order to detect and correct population stratification, we used the EIGENSTRAT software (30, 57). The software applies principal components analysis to genotype data and calculates eigenvalues, which are expected to include large values if the population is stratified. To infer population structure, $P$-values are calculated for eigenvalues under the null hypothesis of no stratification using TW statistics. Multiple correlated SNPs, for example, those in LD, also cause a large eigenvalue, and hence SNPs having a multiple correlation coefficient $> 0.5$ were pruned, in addition to excluding SNPs showing moderate case/control association ($P < 0.01$). In total, 117,598 SNPs were selected for the principal component analysis, and five eigenvalues were found to be significant ($P < 0.01$) as in Supplementary Table S12.

Each eigenvalue corresponds to an eigenvector that represents an axis of
population stratification. Only the first eigenvector was correlated with the case/control status (a correlation coefficient of $-0.186$), as illustrated in Supplementary Figure S10. Although cases and controls from the International Medical Center of Japan (379 cases and 503 controls genotyped) were distributed equally, the samples from Kyushu University were found slightly shifted to the left (140 cases alone). This could be due to genetic diversity among the subjects from different regions in Japan and/or some unnoticed differences in experimental setup between two genotyping facilities; samples typed in the International Medical Center of Japan were collected in Tokyo and Osaka, and their environs, and samples typed in Kyushu University were collected in the Kyushu region. Yet the regional genetic diversity appears to be small, because all samples in our study are clustered closely with the JPT samples among the HapMap populations (see Supplementary Figure S8).

Consequently, we corrected the Cochran-Armitage trend test statistic for each SNP according to the eigenvectors thus detected. The $\lambda$ value of genomic-control (31) that could indicate the overall inflation of significance decreased from 1.047 to 1.032 by this EIGENSTRAT correction. The residual inflation was further removed by applying the genomic-control method. In order to boost the power of the GWA scan, the controls were augmented by additional genotype counts for 964 random controls (see below). The cumulative distribution of $P$-values in the first-stage scan after these corrections is plotted in Supplementary Figure S7.

The adjustment by EIGENSTRAT and genomic-control did not change the statistical significance of four SNPs that were identified by GWA study and confirmed in the subsequent stages: the raw and adjusted $P$-values were $2.3 \times 10^{-4}$ and $1.7 \times 10^{-4}$ for rs4712523 ($CDKAL1$), $2.0 \times 10^{-6}$ and $6.1 \times 10^{-6}$ for rs2383208 ($CDKN2A/2B$), $5.1 \times 10^{-4}$ and $1.9 \times 10^{-3}$ for rs2237892 ($KCNQ1$), and $1.5 \times 10^{-5}$ and $1.4 \times 10^{-5}$ for rs10425678 ($PEPD$).
Effect of genetic difference among geographical regions

The subjects in this study were collected at multiple institutions, and if a SNP tested for association has different frequency among regions in Japan, the test statistic can be skewed. To examine this possibility, we reorganized the samples according to regions and compared the allele frequency in controls for the confirmed SNPs in Table 1. As shown in Supplementary Table S13, all SNPs except rs2383208 had no significant regional difference, and the OR was similar whether stratified by regions and analyzed using Mantel-Haenszel methods, or simply pooled. Even when the OR by two methods is equal, the $P$-value for Mantel-Haenszel appears larger than the $P$-value for allele frequency test of the pooled count, because the number of cases and controls differs in each stratum. The SNP rs2383208 had significant regional difference in allele frequency ($P = 0.002$), and the OR decreased from 1.34 to 1.23 when adjusted using the Mantel-Haenszel methods, but still exhibited statistical significance of $P = 1.8 \times 10^{-7}$.

For the analysis, the subjects were stratified into three regions. The subjects in ‘Tokyo and multi-district’ are from Tokyo, Nagoya, together with the BioBank samples from nationwide, since the residents in the capital city Tokyo generally originate from all over Japan. The ‘Osaka’ and ‘Fukuoka’ subjects are from the respective cities and their environs. We used the rmeta package for the R software (http://www.r-project.org).

Genotype results for 964 random controls from the public database

In addition to the samples genotyped in our study, we incorporated genotype frequencies in the Japanese general population to boost the power of the GWA scan, yet final results of the study were confirmed with our own data. In the relevant dataset, which was made publicly available from the Genome Medical Database of Japan (GeMDBJ; http://gemdbj.nibio.go.jp), a total of 964 samples were genotyped by the Infinium HumanHap550 BeadArray. We applied quality control of SNPs as adopted in
our study; we excluded SNPs for which [1] genotype call rate, <0.95; [2] genotype call rate, <0.99 and MAF, <0.05; [3] significant deviation ($P < 10^{-6}$) from the Hardy-Weinberg equilibrium; or [4] MAF, <0.001.

**Stage-2 genotyping and analysis**

A total of 1,811 SNPs surpassed the stage-1 threshold, and after removing SNPs mutually in strong LD ($r^2 > 0.9$) to avoid redundancy, 1,674 SNPs were subjected to the follow-up analysis in stage 2; 140 SNPs were genotyped by using the iPLEX assay (Sequenom, Cambridge, MA) and 1,534 SNPs by the Illumina GoldenGate Genotyping Assay (Illumina) according to the manufacturer’s protocol.

We characterized 1,110 cases and 1,014 controls (2,124 in total) and adopted all samples in stage-2 analysis. Quality control criteria for markers were the same as in stage 1. After the quality control, we adopted 1,456 SNPs for stage-2 analysis (73 from iPLEX and 1,383 from GoldenGate). Association testing was performed using the Cochran-Armitage trend test statistic.

**Significance level and power of the GWA scan**

We aimed to identify disease-associated SNPs with an OR of 1.3 or 1.2 with a power of 50% or 10%, respectively. To assess the statistical power that represents the ratio of [true positives / (true positives + false negatives)] in our GWA scan, we simulated how frequently a disease-associated SNP could surpass the cut-off level of the first two stages (stages 1 and 2). Here, we regarded the stage-3 scan as a subsequent replication study. We assumed risk allele frequency (RAF) in the range of 0.2–0.7, the disease prevalence of 0.10 and an additive mode of inheritance. Since the sample size in each stage was pre-defined, we adjusted the significance level as follows: a cut-off level of $P < 0.0025$ was set in the first-stage scan to achieve a power of 53% and 17% for ORs of 1.3 and 1.2, respectively. Also, a cut-off level of $P < 7 \times 10^{-5}$ was set in the
second-stage scan to achieve a power of 49% and 11% for ORs of 1.3 and 1.2, respectively (see Supplementary Table S11).

**Replication of previously-reported SNPs**

In parallel with the GWA study, T2D association was tested in the stage 1 and 2 panels for 17 SNPs from 16 T2D candidate loci previously identified by GWA studies in European-descent populations (6–17). For stage-1 samples, 11 SNPs were included in the HumanHap550 array, and six SNPs were separately assayed by the TaqMan method. For stage-2 samples, ten SNPs were genotyped by the iPLEX assay additionally to 73 SNPs that were selected for the follow-up of GWA study, and seven SNPs were assayed by the TaqMan method. Eight SNPs showing significant \( P < 0.05 \) association in the stage 1+2 samples were further studied in an additional panel of 4,000 T2D cases and 4,889 controls in stage 3. Apart from rs7578597 that did not show statistical significance at this point \( P > 0.05 \) for all stages combined, the remaining seven SNPs were further studied in the entire 12,569 population-based sample including the 4,889 pre-selected controls.

**Haplotype analysis in the associated loci detected by GWA study**

In each loci identified by GWA study and/or replicated after the studies previously reported, we looked if more than one independent SNPs are associated with T2D. After adjusting for genotype effects of the SNP showing the lowest \( P \)-value in a locus, no other SNPs turned out to be significant \( P > 0.01 \). When there were multiple significant SNPs mutually not in strong LD (coefficient \( r^2 < 0.8 \)), we tested whether a haplotype class involving them could exert more significant effects than the individual SNPs. Here, haplotypes were inferred from genotype data in the NIBIO stage 1+2 combined panel (jointly for the 1,629 cases and 1,517 controls) and tested using the PLINK software.

In two associated loci, chromosome 6p22.3 (CDKAL1) and 19p13 (PEPD), a
haplotype class showed more significant association than an individual SNP as below.

In the CDKAL1 locus, T2D association is found for two groups of SNPs: one group comprises rs4712523, rs7754840, rs10946398, rs9295475, and rs6906327 that are in strong LD to each other, and another group is rs7756992. The LD estimated between rs7754840 and rs7756992 is $r^2 = 0.66$ in Japanese, and 0.68 in European-derived populations. A risk haplotype class 'GG' showed more significant $P$-value ($P = 5.6 \times 10^{-11}$) than the individual SNPs constituting the haplotype (Supplementary Table S14A).

In the PEPD locus, four SNPs are grouped into two pairs of SNPs that are in complete LD (rs7250175 and rs3786920, $r^2 = 0.99$; rs10425678 and rs11880064, $r^2 = 0.99$; rs7250175 and rs10425678, $r^2 = 0.46$). A protective haplotype class 'CT' showed slightly more significant $P$-value ($P = 7.1 \times 10^{-5}$) than the individual SNPs constituting the haplotype (Supplementary Table S14B).

**Assessment of combined risk of diabetes and pre-diabetes in the general population**

We assessed the combined risk of diabetes by genetic and non-genetic (sex, age, and BMI) factors in a cohort of 12,569 individuals from general population.

We first assessed the effect size of each risk factor by multiple regression analysis with the logarithm of HbA1c (log HbA1c) as a response variable. Explanatory (predictor) variables were sex, age, BMI, and seven robustly-confirmed SNPs: rs4402960 (IGF2BP2), rs4712523 (CDKAL1), rs13266634 (SLC30A8), rs2383208 (CDKN2A/2B), rs1111875 (HHEX), rs7903146 (TCF7L2), and rs5219 (KCNJ11). SNP genotype was coded as 0, 1, or 2 according to the number of risk allele. A total of 12,372 samples with complete data were available for the analysis. The fitted multivariate regression is shown in Supplementary Table S9. $R^2$ denotes the variance of log HbA1c explained by each predictor variable, and it totals 5.3% for all variables included simultaneously in the regression.
Next, we examined how well the ‘actual diabetic state’ in each individual could be estimated by the risk factors of interest. Accumulated risk for each individual was assessed using the above-mentioned regression for HbA1c. We arranged the individuals in order of the risk estimated by multiple regression, sorted the whole population into 20 equal-sized groups (i.e., 5% each), and then examined the distribution of actual HbA1c value and disease status in each group. The diabetic state was assigned by questionnaire information and HbA1c values: individuals who answered in questionnaire to be diabetic or those with HbA1c ≥ 6.1 were classified as 'diabetes (DM)', and others with HbA1c 5.6–6.0 as 'pre-diabetes (pre-DM)' (see above). In Supplementary Figure S6, each group is represented as a vertical bar with the estimated risk increasing from the leftmost to the rightmost bar. Results for the lowest and the highest risk groups are also described in Table 2.

In the above analysis, we used the same set of samples both for the fitting of risk model by regression and for the assessment of actual diabetes prevalence using the resultant model. This may potentially cause overfitting of the model, although the possibility is small owing to the large sample size of 12,372. In order to avoid the overfitting, we also analyzed by randomly selecting half of the population for model fitting and the remaining half for model assessment. From 1,000 random trials, we computed the mean and 95% confidence interval for the prevalence of DM and pre-DM in each risk group. The figures for the highest and the lowest estimated risk groups in Supplementary Table S15 agree well with those in Table 2, suggesting the absence of overfitting.

**The strength of association of a SNP and study power**

We measured the explained variance of a SNP by the coefficient of determination ($R^2$) that represents the ability to detect association signals using the Cochran-Armitage trend test. We calculated $R^2$ for testing association by a linear regression (equivalent to
Cochran-Armitage trend test) with an independent variable \(x\) coding a genotype as 0, 1 or 2 according to the allele copy number, and a dependent variable \(y\) coding disease status as 1 (case) or 0 (control). The \(R^2\) value equals the square of the correlation coefficient for the points \((x, y)\). When testing a total of \(N\) samples under significance level \(\alpha\) for a SNP with \(R^2\), the power equals

\[
\int_{c}^{\infty} F'(1,N-2, NR^2/(1-R^2)) \, dx,
\]

where \(F'(1, N-2, \theta^2)\) is the probability density function for a \(F\)-distribution of \(df\) (degree of freedom) = 1 and \(N-2\) and non-centrality parameter \(\theta^2\), and

\[
\alpha = \int_{c}^{\infty} F(1,N-2) \, dx,
\]

where \(F(1, N-2)\) is the probability density function for a \(F\)-distribution of \(df = 1\) and \(N-2\) [Reference 58, Section 28.28] [Reference 59, Example 8.4]. When \(R^2 = 0.008, 0.004,\) and \(0.002\), the necessary sample size to achieve 80% power is \(N = 4,300, 8,600,\) and \(17,200\) for \(\alpha = 5 \times 10^{-7}\), and \(N = 1,000, 2,000,\) and \(3,900\) for \(\alpha = 0.05\). The power for other combinations of \(N\) and \(\alpha\) are listed in Supplementary Table S7. For the estimation of \(R^2\) of a SNP from RAF and odds ratio (OR), we assumed additive mode-of-inheritance, 10% disease prevalence, and equal-sized cases and controls for a study.

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Figure S1

Graphical summary of stage 1 association results. Horizontal axis is the physical position of each SNP on a chromosome, and the vertical axis is the minus logarithm to base 10 of P-value for the Cochran-Armitage trend test adjusted by EIGENSTRAT and genomic-control. The red SNPs examined in stage 2 had $P<0.0025$ either in trend test or its combination with linkage analysis. The red SNPs distributed lower in the plots showed modest association in trend test but were noticeable in linkage scan.
Figure S2

Meta-analysis of type 2 diabetes association in Japanese and European-derived populations. We performed meta-analysis with the previous studies by three groups in Japanese. The estimate and 95% confidence interval of odds ratio is illustrated in the forest plots. See Supplementary Information for detail. Genotype counts for each SNP is shown in Supplementary Table S4.

(continues to next page)
Figure S2 (continued)

**HHEX rs1111875**
- NIBI combined (5629, 6912)
- Horikoshi et al. (864, 864)
- Omori et al. (1630, 1064)
- Horikawa et al. (1921, 1622)
- **Japanese combined**
  - European (14586, 17968)

**TCF7L2 rs7903146**
- NIBI combined (5629, 6912)
- Horikoshi et al. (1174, 823)
- Hayashi et al. (1630, 1064)
- Miyake et al. (2214, 1873)
- **Japanese combined**
  - European (14586, 17968)

**KCNJ11 rs5219**
- NIBI combined (5629, 6912)
- Horikoshi et al. (864, 864)
- Omori et al. (1630, 1064)
- **Japanese combined**
  - European (14586, 17968)

**FTO rs8050136**
- NIBI stages 1+2 (1629, 1517)
- Horikoshi et al. (864, 864)
- Omori et al. (1630, 1064)
- **Japanese combined**
  - European (14586, 17968)
Figure S3

Linkage disequilibrium (LD) pattern in the European and Japanese populations at loci associated with type 2 diabetes. In the HapMap CEU (top) and JPT (bottom) populations, a red box indicates a SNP pair with $r^2>0.5$. A region of 200kb centered at the most significant SNP is plotted for the IGF2BP2, SLC30A8, HHEX, TCF7L2 and KCNJ11 loci.

**IGF2BP2**

(continues to next page)
Figure S3 (continued)

SLC30A8

(continues to next page)
Figure S3 (continued)
TCF7L2

Genotyped SNPs

Entrez genes

Genome-Wide Association studies

LD Plot

CEU

JPT

(continues to next page)
Figure S3 (continued)
Figure S4

For each type 2 diabetes susceptibility locus, we compared the strength of linkage disequilibrium (LD) between HapMap CEU and JPT+CHB populations. LD is measured between the most significant index SNP in each locus and other SNPs within 200kb and with minor allele frequency at least 1%. Each non-index SNP is plotted by LD coefficient $r^2$ in 60 unrelated CEU (horizontal axis) and JPT+CHB (vertical axis). LD in CDKAL1 and KCNJ11 is stronger in JPT+CHB, whereas LD in IGF2BP2 and HHEX tends to be stronger in CEU. Also refer to Supplementary Figure S3.
Figure S5

ROC curve for the prediction of type 2 diabetes risk with the use of seven susceptibility variants robustly associated in both our Japanese panel and Europeans. We used the same data as Figure 4. For various thresholds of predicted risk, specificity (horizontal axis) and sensitivity (vertical axis) are plotted. The area under the curve was 0.60. The black line is for prediction by random guess.
Figure S6

Assessment of risk for diabetes and pre-diabetes in the general population. Based on the regression of HbA1c value by SNP genotype, age and sex, the risk for high HbA1c was assessed for each individual using a predictor set of either 1) SNPs, 2) age and BMI, or 3) all. We sorted all individuals by their risk, divided the whole population into 20 equal-sized groups (i.e., 5% each) from low to high risk, and in each group, examined the distribution of actual HbA1c value (left figure) and diabetic status (right figure). Male and female are plotted separately.
Figure S7

The cumulative distribution of P-values in the first stage scan after corrections by the EIGENSTRAT and genomic-control methods. Seven robustly-confirmed SNPs in Table 1 are marked in red and labeled. SNPs above the blue horizontal line were genotyped in stage 2 analysis.
Figure S8

Ethnicity of stage 1 samples compared with HapMap populations. Each individual corresponds to a point in the multi-dimensional scaling plot which represents similarity between samples. The bottom plot zooms in around points for the stage 1 samples. Both the cases (DM) and controls (NDM) are clustered together with the Japanese in Tokyo (JPT) from HapMap.
Figure S9

Representative signal intensity plots for nine SNPs that emerged at the end of the three stage scan. In each case of 8 SNPs genotyped with Illumina technology and 1 SNP (rs5219) additionally genotyped with TaqMan technology in the stage 1+2 cohort, the positions of data clouds (for three genotype classes) are demonstrated in the same plots, so as to visualize the ease of allelic discrimination.
Figure S10

Plot of the first two eigenvectors from the EIGENSTRAT analysis of stage 1 genotyping.
**Supplementary Table S1. Characteristics of stage 1, stage 2 and stage 3 case and control samples**

| Variables          | Stage 1<sup>a</sup> |          | Stage 2<sup>a</sup> |          | Stage 3<sup>b</sup> | Population-based panel | Whole subjects |
|--------------------|----------------------|----------|----------------------|----------|----------------------|-------------------------|-----------------|
|                    | Cases | Controls | Cases | Controls | Cases | Controls | Cases | Controls | Cases | Controls | Cases | Controls | Whole subjects |
| Number             | 519    | 503      | 1,110 | 1,014      | 4,000 | 4,889     | 12,569 |          |        |          |        |          |                 |
| Sex Ratio (M / F)  | 315 / 204 | 264 / 239 | 613 / 497 | 542 / 472 | 2,526 / 1,474 | 2,259 / 2,630 | 5,671 / 6,898 |          |        |          |        |          |                 |
| Age at examination (yr) | 66.6 ± 9.8 | 64.7 ± 6.8 | 62.7 ± 11.7 | 71.1 ± 9.6 | 62.3 ± 10.4 | 63.8 ± 5.8 | 62.6 ± 6.8 |          |        |          |        |          |                 |
| BMI (kg/m<sup>2</sup>) | 24.5 ± 3.6 | 23.3 ± 3.1 | 23.3 ± 3.9 | 23.0 ± 3.1 | —         | 22.6 ± 2.8 | 23.1 ± 2.9 |          |        |          |        |          |                 |
| Fasting Plasma Glucose (mmol/l)<sup>c</sup> | 8.44 ± 2.65 | 5.22 ± 0.46 | 8.96 ± 3.38 | 5.06 ± 0.47 | —         | —         | —         |          |        |          |        |          |                 |
| HbA1c (%)          | 7.26 ± 1.25 | 5.20 ± 0.28 | 7.78 ± 1.85 | 5.40 ± 0.34 | —         | 4.79 ± 0.20 | 5.23 ± 0.77 |          |        |          |        |          |                 |

<sup>a</sup> Stage 1 and stage 2 case and control subjects were selected according to the identical criteria described in the methods. Because of the pre-determined policy of collaborative study in analyzing the relevant samples, clinical characteristics other than T2D affection status are not provided for 140 cases in the stage 1 scan; therefore, the characteristics are shown for the remaining 379 samples out of 519.

<sup>b</sup> The stage 3 panel comprises T2D cases and a population-based panel; subjects in the population-based panel are participants of medical checkup in the epidemiological survey that has been organized by Kyushu University. Controls in the stage 3 panel are part of the population-based panel (see the methods section). Because of the pre-determined policy of collaborative study in analyzing the relevant samples, clinical characteristics other than T2D affection status and age are not provided for 4,000 case samples in the stage 3 scan, which have been collected as part of the Biobank Japan project (Nakamura, Y. Clin. Adv. Hematol. Oncol. 5, 696-697 (2007)).

<sup>c</sup> Not fasting plasma glucose but HbA1c levels were measured for all subjects in the population-based panel of stage 3.
### Supplementary Table S2. SNP genotyping in the present T2D study.

| Assay        | Stage 1 | Stage 2 | Stage 3  |
|--------------|---------|---------|----------|
|              | HumanHap550 | TaqMan | iPLEX    | GoldenGate | TaqMan | TaqMan | TaqMan |
| # of SNPs assayed | 555,352 | 6       | 150      | 1534 | 7 | 7 | 16 |
| SNPs typed successfully<sup>a</sup> | 482,625 | 6 | 83 | 1383 | 7 | 7 | 16 |
| Number      | 87%     | 100%    | 55%      | 90%  | 100% | 100% | 100% |
| Avg. call rate | 0.998 | 0.975 | 0.987 | 0.998 | 0.995 | 0.998 | 0.996 |
| Std. dev. of call rate | 0.006 | 0.002 | 0.011 | 0.005 | 0.002 | 0.001 | 0.002 |

<sup>a</sup>We removed SNPs with genotype call rate <0.95, or <0.99 and minor allele frequency (MAF) <0.05, or significant ($P < 1 \times 10^{-6}$) deviation from Hardy-Weinberg equilibrium in the controls, or MAF <0.001.

<sup>b</sup>Samples from Kyushu University (140 cases) are not included.

<sup>c</sup>For seven SNPs that were chosen for replication study and confirmed in both European-descent and Japanese populations, all the general population samples (n=12,569) were genotyped, whereas part of them (n=4,889) were genotyped as controls for 16 SNPs that survived after stages 1 and 2 scans.
In the 7p region, rs2329487 was genotyped in substitution for rs2244480, because these two SNPs were in LD ($r^2=0.64$) to each other and modest T2D association ($p=0.033$) was shown for rs2329487 in DIAGRAM data.

### Supplementary Table S3. Summary of association with T2D for SNPs surpassing stage 2 of GWA scan (Cochran-Armitage trend test $P$-value $<7E-05$ in stage 1+2 combined with Japanese general population)

| SNP          | Gene symbol | Minor allele | Chr    | Minor allele frequency | T2D Case | T2D Control | Type of test | Stage 2 $P$-value | Stage 2 Odds ratio | Minor allele frequency | Stage 2 Odds ratio | Minor allele frequency | Stage 2 Odds ratio |
|--------------|-------------|--------------|--------|------------------------|----------|-------------|--------------|-------------------|-------------------|----------------------|----------------------|----------------------|----------------------|
| rs10425678   |             |              | 7      | C                      | 0.20     | 0.17        | One-tailed    | 0.002             | 1.14              | 0.20                 | 0.17                 | 0.20                 | 0.17                 |
| rs13025789   |             |              | 7      | G                      | 0.26     | 0.23        | One-tailed    | 0.02             | 1.16              | 0.26                 | 0.23                 | 0.26                 | 0.23                 |
| rs7212633    |             |              | 7      | T                      | 0.23     | 0.20        | One-tailed    | 0.11             | 1.12              | 0.23                 | 0.20                 | 0.23                 | 0.20                 |
| rs2329487    |             |              | 7      | T                      | 0.26     | 0.23        | One-tailed    | 0.02             | 1.16              | 0.26                 | 0.23                 | 0.26                 | 0.23                 |
| rs347313     |             |              | 7      | C                      | 0.20     | 0.17        | One-tailed    | 0.002             | 1.14              | 0.20                 | 0.17                 | 0.20                 | 0.17                 |

*Stage 1 data was removed from the table for clarity.*
| rs1277979 | 1 | 3 | 43 | 1557 | 1 | 27 | 1927 | 0.003 | 0.088 | 0.001 | 0.037 | 0.082 | 0.003 | 0.019 | 1.51 (1.07, 1.77) | 3.28E-01 | 7.42E-01 | 7.42E-01 | 6.26E-01 | 0.0001 |
| rs7756992 | 1 | 2 | 45 | 555 | 45 | 45 | 10 | 0.004 | 0.003 | 0.005 | 0.005 | 0.019 | 0.005 | 0.018 | 3.34 (2.92, 3.83) | 2.31E-01 | 1.86E-01 | 1.86E-01 | 1.39E-01 | 0.032 |
| rs7578597 | 1 | 1 | 116 | 139 | 116 | 128 | 116 | 3.34 | 0.001 | 0.005 | 0.005 | 1.95 | 0.12 (1.03, 1.37) | 0.05E-02 | 6.72E-02 | 6.72E-01 | 5.82E-02 | 0.014 |
| rs10923931 | 1 | 1 | 116 | 139 | 116 | 128 | 116 | 3.34 | 0.001 | 0.005 | 0.005 | 1.95 | 0.12 (1.03, 1.37) | 0.05E-02 | 6.72E-02 | 6.72E-01 | 5.82E-02 | 0.014 |
| rs1277979 | 4 | 12 | 120 | 230 | 0.001 | 0.005 | 0.005 | 3.63 | 0.001 | 0.005 | 0.005 | 1.95 | 0.12 (1.03, 1.37) | 0.05E-02 | 6.72E-02 | 6.72E-01 | 5.82E-02 | 0.014 |
| rs7578597 | 4 | 12 | 120 | 230 | 0.001 | 0.005 | 0.005 | 3.63 | 0.001 | 0.005 | 0.005 | 1.95 | 0.12 (1.03, 1.37) | 0.05E-02 | 6.72E-02 | 6.72E-01 | 5.82E-02 | 0.014 |
| rs10923931 | 4 | 12 | 120 | 230 | 0.001 | 0.005 | 0.005 | 3.63 | 0.001 | 0.005 | 0.005 | 1.95 | 0.12 (1.03, 1.37) | 0.05E-02 | 6.72E-02 | 6.72E-01 | 5.82E-02 | 0.014 |

**Note:** Alleles according to Moin et al.
Genotypes are denoted RR, RP and PP, where 'R' is the risk allele, and 'P' is the protective allele.

| rs   | NIBI combined (1809, 1805) | 450 | 232 | 228 | 319 | 167 | 64 | 37 | 55 |
|------|---------------------------|-----|-----|-----|-----|-----|-----|-----|-----|
| rs5215 (rs2237892) | 1 | 91 | 89 | 6 | 0 | 0.01 | 0.02 | 0.02 | 0.02 |
| rs1111875 | 3 | 142 | 144 | 8 | 4 | 0 | 0.01 | 0.02 | 0.02 |

NIBI stages 1+2 with general population (5629, 7370) 245, 435 212, 210 31, 14 101, 92 17, 12 3, 3 0.003 0.001

NIBI stages 1+2 with general population (1629, 1517) 245, 435 212, 210 31, 14 101, 92 17, 12 3, 3 0.003 0.001

NIBI stage 1 with general population (519, 503) 176, 176 176, 176 176, 176 176, 176 176, 176 176, 176 0.003 0.001

NIBI stages 1+2 (1629, 1517) 245, 435 212, 210 31, 14 101, 92 17, 12 3, 3 0.003 0.001

NIBI stage 2 (1110, 1014) 245, 435 212, 210 31, 14 101, 92 17, 12 3, 3 0.003 0.001

NIBI stage 1 with general population (519, 503) 176, 176 176, 176 176, 176 176, 176 176, 176 176, 176 0.003 0.001

NIBI stages 1+2 (1629, 1517) 245, 435 212, 210 31, 14 101, 92 17, 12 3, 3 0.003 0.001

NIBI stage 2 (1110, 1014) 245, 435 212, 210 31, 14 101, 92 17, 12 3, 3 0.003 0.001

NIBI stage 1 with general population (519, 503) 176, 176 176, 176 176, 176 176, 176 176, 176 176, 176 0.003 0.001

NIBI stages 1+2 (1629, 1517) 245, 435 212, 210 31, 14 101, 92 17, 12 3, 3 0.003 0.001
The predictor variable for a SNP genotype is coded by the copy number of minor allele. The predictor variable of 'BMI' takes a raw BMI value, and 'BMIge25' is a categorical variable indicating if BMI is greater or equal to 25. We tested three models of regression with the predictor(s) as SNP alone, SNP with BMI, and SNP with BMIge25. The models are separated by horizontal lines in the table. Results are shown for an individual stage or their combinations,
Supplementary Table S6. Comparison of T2D Association of 19 SNPs between Japanese and European-decent populations.

| SNP | Chr | Position (bp) | Region | Risk allele / non-risk allele | Japanese | European-decent | Reference |
|-----|-----|---------------|--------|-------------------------------|----------|-----------------|-----------|
| rs4129603 | 3 | 185,944,389 | NOTCH2-ADAM30 | C/T | 0.310 | 1.16 (1.11–1.21) | 0.0008 | TCF2 and ADAMTS9 | 0.00016 |
| rs4129604 | 5 | 20,725,543 | CDKL1F | G/A | 0.407 | 1.30 (1.21–1.32) | 0.0006 | ADAMTS9 | 0.00015 |
| rs12888034 | 8 | 118,223,964 | LCLCAM | G/T | 0.570 | 1.20 (1.15–1.25) | 0.0037 | TCF2 and ADAMTS9 | 0.00012 |
| rs2283228 | 9 | 22,122,078 | CDKN2A/B | A/G | 0.553 | 1.29 (1.24–1.35) | 0.0002 | TCF2 and ADAMTS9 | 0.00012 |
| rs1191775 | 10 | 94,942,862 | HHEX | C/T | 0.275 | 1.23 (1.16–1.29) | 0.0003 | ADAMTS9 | 0.00011 |
| rs708132 | 11 | 57,759,577 | HHEX | A/G | 0.457 | 1.34 (1.25–1.45) | 0.0006 | CDKN2A/B, ADAMTS9 | 0.00011 |
| rs708129 | 12 | 23,177,299 | HHEX | T/C | 0.549 | 1.39 (1.30–1.48) | 0.0002 | CDKN2A/B, ADAMTS9 | 0.00011 |

Japanese population

- Control sample allele freq = 0.310
- OR (95% CI) = 1.16 (1.11–1.21)
- P (trend) = 0.0008
- Population attributable risk = 0.00016

European-decent population

- Control sample allele freq = 0.407
- OR (95% CI) = 1.30 (1.21–1.32)
- P (trend) = 0.0006
- Population attributable risk = 0.00015

Population attributable risk is calculated by meta-analysis of data in DIAGRAM and those presented by Yasuda et al. and Unoki et al. (2008), from which the control risk allele frequency in European-decent populations is derived.

Woolf's test of heterogeneity for OR in Japanese and European-decent populations.

- Test statistic = 2.34
- P-value = 0.127

Association weaker in Japanese than in European-decent populations

- OR (95% CI) = 0.141
- P-value = 0.202

Association results (OR and P-value) for rs2237892 in the TCF2 locus are calculated by meta-analysis of data in DIAGRAM and those presented by Sladek (2007) Nature and Yasuda et al. (2008) Nat Genet.

Results of T2D association are compared between Japanese and European-decent populations for a total of 19 SNPs with significant evidence for association, which has been reported originally in large-scale European-decent populations except for HHEX.
### Supplementary Table S7. Power for testing a SNP with coefficient of determination $R^2$ in $N$ samples, half cases and half controls, under a significance level of $\alpha$ (see Supplementary Information for details).

| $R^2$  | Odds Ratio | Corresponding SNP from meta-analysis in Japanese | 5x10^{-7} | 0.05 |
|--------|------------|-----------------------------------------------|-----------|------|
|        | Risk allele frequency | | Sample size (N) | Sample size (N) |
| 0.008  | 1.34       | 1.29 | 1.41 | 0.014 | 0.453 | 1.000 | 1.000 | 0.810 | 0.998 | 1.000 | 1.000 |
| 0.004  | 1.24       | 1.20 | 1.27 | 0.001 | 0.059 | 0.904 | 1.000 | 0.517 | 0.934 | 1.000 | 1.000 |
| 0.002  | 1.16       | 1.13 | 1.18 | 0.0001| 0.005 | 0.290 | 0.904 | 0.293 | 0.688 | 0.994 | 1.000 |
| 0.001  | 1.12       | 1.09 | 1.12 | $FTO$, rs8050136 | 2.8E-05 | 0.0005 | 0.031 | 0.290 | 0.170 | 0.410 | 0.886 | 0.994 |
| 0.0004 | 1.07       | 1.06 | 1.07 | $PPARG$, rs1801282 | 5.5E-06 | 4.2E-05 | 0.001 | 0.014 | 0.097 | 0.195 | 0.516 | 0.808 |
| 0.0003 | 1.06       | 1.05 | 1.06 | $EXT2$, rs3740878 | 3.7E-06 | 2.3E-05 | 0.0005 | 0.005 | 0.085 | 0.158 | 0.410 | 0.688 |

For the reader's reference, the observed power of $<0.5$, i.e., an arbitrarily defined level of insufficient study power, is obscured in gray for a series of representative situations in the table.
Supplementary Table S8. Results of T2D association of 7 previously-reported SNPs with suggestive evidence in Japanese [from Yasuda et al. (2008) Nat Genet 40:1092, Table 1]

| Original SNP rs#* | Chr | SNP rs# | Position (bp) | Minor allele frequency | Odds ratio | (95% CI) | P trend |
|-------------------|-----|---------|---------------|------------------------|------------|----------|---------|
| rs2250402         | 15  | rs2250402 | 38109844      | 0.229                  | 1.10       | (0.89 – 1.36) | 0.376   |
| rs2307027         | 12  | rs2307027 | 51490881      | 0.201                  | 1.04       | (0.82 – 1.32) | 0.749   |
| rs3741872 (r^2=0.839) | 12  | rs2293040 | 31346021      | 0.257                  | 1.17       | (0.95 – 1.43) | 0.141   |
| rs574628          | 20  | rs574628  | 840948        | 0.393                  | 1.02       | (0.85 – 1.22) | 0.842   |
| rs2233647 (r^2=0.889) | 6   | rs11758426 | 34611316      | 0.132                  | 0.90       | (0.70 – 1.15) | 0.404   |
| rs3785233 (r^2=0.781) | 16  | rs7204945  | 7608397       | 0.201                  | 1.04       | (0.83 – 1.29) | 0.734   |
| rs2075931 (r^2=1) | 1   | rs1883109  | 34562006      | 0.349                  | 1.20       | (1.00 – 1.44) | 0.061   |

The results were derived from the stage 1 panel in the present GWA study (519 cases vs. 503 controls).

*In case the identical SNPs were not genotyped in the stage 1 of GWA study, the results for the alternative SNPs in high LD are shown.
**Supplementary Table S9. Multiple regression of the logarithm of HbA1c in the general population.**

|                                 | Regression coefficient, assuming multiplicative effect on HbA1c (95%CI) | P-value  | $R^2$ |
|---------------------------------|-------------------------------------------------------------------------|----------|-------|
| Sex (male)                      | 1.011 (1.006 – 1.015)                                                  | 7.8E-07  | 0.0047|
| Age                             | 1.002 (1.002 – 1.002)                                                  | 3.9E-41  | 0.0143|
| BMI                             | 1.006 (1.005 – 1.007)                                                  | 5.5E-54  | 0.0172|
| rs4712523                       | 1.010 (1.007 – 1.013)                                                  | 2.2E-11  | 0.0036|
| rs2383208                       | 1.011 (1.008 – 1.014)                                                  | 1.6E-13  | 0.0042|
| rs4402960                       | 1.007 (1.004 – 1.010)                                                  | 1.9E-05  | 0.0014|
| rs13266634                      | 1.009 (1.006 – 1.012)                                                  | 7.7E-09  | 0.0026|
| rs1111875                       | 1.006 (1.003 – 1.010)                                                  | 2.4E-04  | 0.0010|
| rs7903146                       | 1.024 (1.017 – 1.032)                                                  | 4.8E-10  | 0.0029|
| rs5219                          | 1.005 (1.002 – 1.008)                                                  | 2.4E-03  | 0.0007|
Supplementary Table S10. Effects of control selection criteria and study basis (meta-analysis and origin) on the odds ratio in case-control comparison

| rs#   | Region    | Nested case-control comparison (vs. 740 diabetic cases) within the same population | Meta-analysis in JPN | Case/control study in Chinese & Korean (ref.23) |
|-------|-----------|-----------------------------------------------------------------------------------|----------------------|-----------------------------------------------|
|       |           | Non-diabetics controls (N=4,889)                                                  | Combined controls (N=8,484-10,672) | Combined controls (N=3,678)                   |
|       |           | Control subjects excl. diabetics (N=11,829)                                        |          |                                               |
| rs4402960 | IGF2BP2  | 1.27 (1.13 – 1.43)                                                                | 1.16 (1.11 – 1.21)   | 1.14 (1.06 – 1.23)                            |
| rs4712523 | CDKAL1    | 1.36 (1.21 – 1.52)                                                                | 1.26 (1.21 – 1.32)   | 1.28 (1.19 – 1.37)                            |
| rs13266634 | SLC30A8  | 1.27 (1.13 – 1.43)                                                                | 1.20 (1.15 – 1.25)   | 1.13 (1.05 – 1.21)                            |
| rs2383208 | CDKN2A/B  | 1.37 (1.22 – 1.54)                                                                | 1.29 (1.24 – 1.35)   | 1.29 (1.20 – 1.38)                            |
| rs1111875 | HHEX      | 1.21 (1.07 – 1.36)                                                                | 1.23 (1.18 – 1.29)   | 1.16 (1.07 – 1.24)                            |
| rs7903146 | TCF7L2    | 2.04 (1.61 – 2.58)                                                                | 1.54 (1.36 – 1.74)   | 1.35 (1.10 – 1.67)                            |
| rs5219  | KCNJ11    | 1.17 (1.04 – 1.31)                                                                | 1.14 (1.02 – 1.27)   | N/A                                            |

From the population-based subjects in stage 3 (N=12,569), the controls were chosen as either (1) non-diabetics with HbA1c ≤5.0 or (2) the remaining subjects after excluding diabetics. These controls were compared with diabetic cases (N=740) who were under medication or HbA1c ≥7.0. Here, the diabetic cases in this general population were not included in the meta-analysis in Japanese.

Even when relatively generous criteria were adopted for control selection, i.e., simply excluding diabetics from the entire population (in the middle columns), the ORs were almost comparable to those calculated by meta-analysis in Japanese (in the right columns) (see Supplementary Figure S2 and Supplementary Table S4). Increased and decreased ORs (differences ≥0.5) were colored in red and blue, respectively.

When compared to the ORs reported by Ng et al. (N=6,719, reference 23), no significant differences were detected between the two studies by Woolf's method (P >0.05), while the ORs tended to be smaller for SLC30A8 and TCF7L2 in the study by Ng et al., where rs7754840 for CDKAL1 and rs10811661 for CDKN2A/B were used.
### Supplementary Table S11A. Power of the first stage in the present GWA study.

| RAF | OR 1.3 | OR 1.2 | OR 1.15 |
|-----|--------|--------|---------|
| 0.2 | 0.53   | 0.17   | 0.08    |
| 0.3 | 0.66   | 0.26   | 0.11    |
| 0.4 | 0.73   | 0.30   | 0.16    |
| 0.5 | 0.74   | 0.29   | 0.13    |
| 0.6 | 0.68   | 0.29   | 0.12    |
| 0.7 | 0.58   | 0.20   | 0.11    |

Samples comprised of 1,629 cases, and 2,481 (=1,517+964) controls; a cut-off level was set at $P < 7 \times 10^{-5}$.

### Supplementary Table S11B. Power of the second stage in the present GWA study.

| RAF | OR 1.3 | OR 1.2 | OR 1.15 |
|-----|--------|--------|---------|
| 0.2 | 0.49   | 0.11   | 0.03    |
| 0.3 | 0.65   | 0.18   | 0.05    |
| 0.4 | 0.72   | 0.24   | 0.08    |
| 0.5 | 0.73   | 0.23   | 0.06    |
| 0.6 | 0.67   | 0.22   | 0.07    |
| 0.7 | 0.56   | 0.14   | 0.05    |

Samples comprised of 519 cases, and 1,467 (=503+964) controls; a cut-off level was set at $P < 0.0025$. 
Supplementary Table S12. Eigenvalues from the EIGENSTRAT analysis in the stage 1 genotyping.

| Number | Eigenvalue | TW Statistics | TW P-value |
|--------|------------|----------------|------------|
| 1      | 1.340      | 75.072         | 2.27E-190  |
| 2      | 1.251      | 8.866          | 1.86E-09   |
| 3      | 1.247      | 6.068          | 1.63E-06   |
| 4      | 1.242      | 3.024          | 1.63E-03   |
| 5      | 1.240      | 2.213          | 7.22E-03   |
| 6      | 1.239      | 1.817          | 0.014      |
| 7      | 1.236      | 0.347          | 0.113      |
| 8      | 1.234      | -0.852         | 0.372      |
| 9      | 1.232      | -1.977         | 0.719      |
| 10     | 1.231      | -2.174         | 0.773      |
Supplementary Table S13. Association of SNPs listed in Table 1, stratified by geographical regions.

| rs#      | Region  | Risk allele / protective allele | Risk allele frequency | Heterozygosity of allele frequency in controls (P) | Heterozygosity of odds ratio (P)* | Mantel-Haenszel* | Pooled       |
|----------|---------|--------------------------------|-----------------------|--------------------------------------------------|----------------------------------|------------------|--------------|
|          |         |                                 | Tokyo and multi-district | Osaka    | Fukuoka   | Tokyo and multi-district | Osaka    | Fukuoka   |                |                |
|          |         |                                 | cases (4837) | controls (1107) | cases (652) | controls (410) | cases (140) | controls (5395) | cases (5629) | controls (6912) | cases (5629) | controls (6912) | cases (5629) | controls (6912) |
| rs4712523 | CDKAL1  | G / A                           | 0.463 | 0.465 | 0.492 | 0.393 | 0.446 | 0.409 | 0.456 | 0.407 | 0.684 | 0.182 | 1.29 | (1.20, 1.40) | (1.21, 1.33) |
| rs2383208 | CDKN2A/B| A / G                           | 0.620 | 0.588 | 0.652 | 0.548 | 0.618 | 0.546 | 0.623 | 0.553 | 0.002 | 0.010 | 1.23 | (1.14, 1.34) | (1.27, 1.41) |
| rs4402960 | IGFBP2  | T / G                           | 0.337 | 0.314 | 0.349 | 0.313 | 0.359 | 0.309 | 0.339 | 0.310 | 0.885 | 0.634 | 1.14 | (1.05, 1.24) | (1.08, 1.21) |
| rs13266634| SLC30A8 | C / T                           | 0.619 | 0.577 | 0.605 | 0.543 | 0.625 | 0.571 | 0.618 | 0.570 | 0.235 | 0.714 | 1.22 | (1.13, 1.32) | (1.16, 1.28) |
| rs111875  | HHEX    | C / T                           | 0.311 | 0.286 | 0.329 | 0.284 | 0.361 | 0.272 | 0.314 | 0.275 | 0.353 | 0.094 | 1.19 | (1.09, 1.29) | (1.15, 1.28) |
| rs7903146 | TCF7L2  | T / C                           | 0.055 | 0.035 | 0.037 | 0.032 | 0.050 | 0.036 | 0.053 | 0.035 | 0.835 | 0.501 | 1.52 | (1.25, 1.87) | (1.36, 1.74) |
| rs2237892 | KCNQ1   | C / T                           | 0.659 | 0.615 | 0.668 | 0.605 | 0.696 | 0.588 | 0.661 | 0.594 | 0.049 | 0.113 | 1.27 | (1.17, 1.37) | (1.27, 1.41) |
| rs5219   | KCNJ11  | T / C                           | 0.366 | 0.363 | 0.408 | 0.336 | NA    | 0.355 | 0.371 | 0.355 | 0.386 | 0.005 | 1.08 | (0.99, 1.17) | (1.01, 1.13) |
| rs10425678| PEPD    | C / T                           | 0.282 | 0.266 | 0.292 | 0.226 | 0.329 | 0.261 | 0.285 | 0.260 | 0.065 | 0.031 | 1.18 | (1.07, 1.28) | (1.14, 1.40) |

*The data for rs5219 is based on two strata 'Tokyo and multi-district' and 'Osaka', because the genotype for the cases in 'Fukuoka' stratum is missing. The corresponding figures are denoted in italic font.
### Supplementary Table S14A. Association of haplotypes in the CDKAL1 locus.

| SNP       | Chr | Position | Minor allele | Major allele | Minor allele frequency | P-value | OR   |
|-----------|-----|----------|--------------|--------------|------------------------|---------|------|
| rs4712523 | 6   | 20765543 | G            | A            | 0.481                  | 3.4E-10 | 1.38 |
| rs7756992 | 6   | 20787688 | G            | A            | 0.523                  | 2.3E-09 | 1.35 |

| SNPs constituting haplotype | Haplotype class | Haplotype class frequency | P-value |
|-----------------------------|-----------------|---------------------------|---------|
| rs4712523 | rs7756992       | GG                        | 0.454   | 3.4E-10  |
| rs4712523 | rs7756992       | AG                        | 0.070   | 0.27     |
| rs4712523 | rs7756992       | GA                        | 0.027   | 0.38     |
| rs4712523 | rs7756992       | AA                        | 0.450   | 2.2E-08  |

### Supplementary Table S14B. Association of haplotypes in the PEPD locus.

| SNP       | Chr | Position | Minor allele | Major allele | Minor allele frequency | P-value | OR   |
|-----------|-----|----------|--------------|--------------|------------------------|---------|------|
| rs7250175 | 19  | 38680322 | T            | C            | 0.224                  | 0.00017 | 1.27 |
| rs10425678| 19  | 38669236 | C            | T            | 0.295                  | 0.00035 | 1.23 |

| SNPs constituting haplotype | Haplotype class | Haplotype class frequency | P-value |
|-----------------------------|-----------------|---------------------------|---------|
| rs7250175 | rs10425678      | TC                        | 0.196   | 0.0006  |
| rs7250175 | rs10425678      | CC                        | 0.099   | 0.33    |
| rs7250175 | rs10425678      | TT                        | 0.028   | 0.17    |
| rs7250175 | rs10425678      | CT                        | 0.878   | 7.1E-05 |
**Supplementary Table S15. Combined risk of diabetes and pre-diabetic status corrected for overfitting.**

|                        | Prevalence of DM (95% CI) | Prevalence of pre-DM (95% CI) | Prevalence of DM or pre-DM (95% CI) |
|------------------------|---------------------------|-------------------------------|-------------------------------------|
| **Male**               |                           |                               |                                     |
| Highest risk group (5%) predicted by |                           |                               |                                     |
| All variables          | 0.26 (0.21, 0.32)         | 0.09 (0.05, 0.13)             | 0.35 (0.29, 0.42)                  |
| SNP genotypes          | 0.27 (0.22, 0.34)         | 0.06 (0.03, 0.10)             | 0.34 (0.27, 0.40)                  |
| Age and BMI            | 0.19 (0.14, 0.24)         | 0.14 (0.10, 0.18)             | 0.33 (0.27, 0.39)                  |
| Lowest risk group (5%) predicted by |                           |                               |                                     |
| All variables          | 0.08 (0.04, 0.12)         | 0.04 (0.01, 0.06)             | 0.12 (0.08, 0.16)                  |
| SNP genotypes          | 0.11 (0.06, 0.15)         | 0.05 (0.02, 0.08)             | 0.15 (0.11, 0.20)                  |
| Age and BMI            | 0.08 (0.05, 0.12)         | 0.03 (0.01, 0.04)             | 0.11 (0.06, 0.15)                  |
| **Female**             |                           |                               |                                     |
| Highest risk group (5%) predicted by |                           |                               |                                     |
| All variables          | 0.22 (0.17, 0.27)         | 0.12 (0.08, 0.16)             | 0.34 (0.28, 0.40)                  |
| SNP genotypes          | 0.16 (0.12, 0.20)         | 0.08 (0.05, 0.11)             | 0.24 (0.19, 0.28)                  |
| Age and BMI            | 0.16 (0.12, 0.20)         | 0.12 (0.08, 0.16)             | 0.28 (0.23, 0.33)                  |
| Lowest risk group (5%) predicted by |                           |                               |                                     |
| All variables          | 0.01 (0.00, 0.02)         | 0.01 (0.00, 0.02)             | 0.02 (0.01, 0.04)                  |
| SNP genotypes          | 0.03 (0.01, 0.05)         | 0.05 (0.02, 0.08)             | 0.08 (0.05, 0.11)                  |
| Age and BMI            | 0.02 (0.01, 0.05)         | 0.01 (0.00, 0.02)             | 0.04 (0.01, 0.06)                  |