ONLINE METHODS

GWAS meta-analysis of 2 hour glucose. *Discovery samples, genotyping, imputation and genome-wide analysis.* Informed consent was obtained from all study participants and study protocols were approved by each participating institution's ethical committee. Details of clinical characteristics, genotyping, quality control, imputation and genome-wide association analysis methods for each study sample are provided in **Supplementary Table 1**. Diabetic individuals (previously diagnosed, on diabetic medication and/or fasting plasma glucose ≥7 mmol/l) were excluded from the study. Genotypes were generated for nondiabetic individuals using high-density SNP arrays and imputed for ungenotyped SNPs using phased HapMap II genotypes from the 60 European (CEU) HapMap founders using IMPUTE (see URLs), which determines the probability distribution of missing genotypes conditional on a set of known haplotypes and an estimated fine-scale recombination map, or MACH (see URLs), which determines the probability distribution of missing genotypes conditional on a set of known haplotypes and simultaneously estimates the fine-scale recombination map[30,31].

Each study performed individual uniform genome-wide association analyses and submitted summary statistics in a standardized format to the 2 hour glucose writing and analysis groups. Individual-level genotype data was not shared across studies. An additive genetic model with age, sex and study-specific covariates (primarily center and/or principal components) was used to test for genetic association with the untransformed 2 hour glucose trait value, as it was close to being normally distributed.

Association analyses in each study were performed with or without adjustment for BMI and fasting glucose levels. Only stage 1 and 2 CHS GWAS data were available for inclusion in discovery meta-analysis, and therefore stage 3 data were used for *in silico* follow up of 29 SNPs only. Therefore, CHS is listed as both a discovery and replication cohort.

Meta-analyses of discovery GWAS. We used meta-analyses to combine summary statistics from each of the nine GWAS. Before meta-analysis, GWAS results from each study were filtered to include SNPs with genotype call rate >95%, Hardy-Weinberg equilibrium P value $>10^{-6}$ and minor allele frequency >1%; imputed SNPs were filtered to satisfy proper_info > 0.4 (IMPUTE) or r^2 hat > 0.3 (MACH). Genome-wide association effect estimates for all SNPs from each analysis for the nine studies (ARIC, BLSA, CHS, Colaus, DGI, Fenland, FHS, FUSION and Sorbs) were then combined using a fixed effects inverse variance meta-analysis as implemented in the program METAL (see URLs).

SNP prioritization criteria. From four interim z-score based genome-wide association meta-analyses, 29 independent SNPs with association $P < 10^{-5}$ with 2 hour glucose (with or without BMI adjustment) or 2 hour glucose adjusted for fasting glucose (with or without BMI adjustment) were selected for replication genotyping, and 8 SNPs with greater statistical significance ($1.8 \times 10^{-13} < P < 2 \times 10^{-6}$) and 2 SNPs with biological plausibility (SNPs from the EPHA4 and LRP1B regions, $P < 10^{-5}$) were prioritized for genotyping in replication samples that could contribute only a smaller number of directly genotyped SNPs to this study. Among SNPs showing evidence for association and in strong linkage disequilibrium, we elected to follow up only the most significant SNP, although proxies were provided to the follow-up groups in case the genotyping assay for the primary SNP failed. SNPs with $r^2 < 0.3$ and at a distance of 500 kb apart or greater were treated as independent association signals. Prioritized SNPs included those previously associated with T2D and fasting glucose (TCF7L2 and GCKR).

Follow-up samples, genotyping, analysis and global meta-analysis. Informed consent was obtained from all study participants and study protocols were approved by each participating institution's ethical committee. Clinical information, genotyping, quality control and analysis methods for 6,958–30,620 samples from 17 studies used for follow-up genotyping are listed in **Supplementary Table 1**. The CHS and French Obese Adult cohorts contributed *in silico* imputed and genotype SNP association results for all 29 SNPs from their GWAS. SNPs with genotype call rates >90%, Hardy-Weinberg equilibrium P value $>10^{-6}$ and minor allele frequency >1% were included in each follow-up association study. In cases where the index SNP failed genotyping or did not efficiently design with our SNPs in an assay pool, a correlated proxy (having $r^2 > 0.80$) SNP was substituted. A fixed-effects inverse-variance meta-analysis on replication data was performed.

We then carried out a combined meta-analysis using the inverse-variance meta-analysis method. Heterogeneity in effect size across studies was estimated using the Q statistic (in METAL). A genome-wide significance threshold of $P = 5 \times 10^{-8}$ in the joint discovery and follow-up samples was applied[32].

Indices of insulin response. *2 hour insulin adjusted for 2 hour glucose.* We examined all discovery and replication samples that had 2 hour insulin measurements (see **Supplementary Table 1** for details on insulin measurements). In a uniform analysis, we tested the SNP or a close proxy from three loci (on *GIPR*, *ADCY5* and *VPS13C*) for additive genetic association with natural logarithm–transformed 2 hour insulin values adjusted for age, sex, and 2 hour glucose levels. These analyses were performed with or without adjustment for BMI. The meta-analysis was conducted using the inverse-variance method in METAL.

Insulinogenic index and $AUC_{insulin/glucose}$. In studies with measures of glucose and insulin at time points other than 120 min during the OGTT, we calculated the insulinogenic index and the ratio of the area under the curve for insulin over the area under the curve for glucose ($AUC_{ins/gluc}$). The insulinogenic index is calculated using the formula (insulin 30 (μU/ml) − insulin 0 (μU/ml))/(glucose 30 (mmol/l) − glucose 0 (mmol/l)) and represents the early insulin secretion phase in response to the oral glucose challenge. The $AUC_{ins/gluc}$ is calculated using the trapezoidal rule[33] using all available time points during the OGTT (minimum of three time points required for our analyses) and represents the integrated insulin response over the course of the OGTT following a standard glucose challenge of 75 g. Both traits were natural log transformed and adjusted for sex, age, study-specific covariates such as study center (with or without adjustment for BMI), and SNP association to phenotype was performed assuming an additive genetic model.

Insulin response to intravenous glucose and incretin effect. Frequently-sampled intravenous glucose tolerance tests and genotypes for *GIPR* rs10423928 were available in four studies with nondiabetic individuals.

In the FUSION study, 564 nondiabetic spouses and offspring ($n = 564$) of T2D index cases were available for analyses[34]. Insulin secretion was assessed as the acute insulin response (AIR) to glucose computed as the incremental area under the insulin curve for the first 10 min. AIR was tested for association with rs10423928 using a regression framework in the context of variance components to account for relatedness among individuals. Models were adjusted for sex, age, age^2 and birth province within Finland. Covariate-adjusted trait values were transformed to approximate univariate normality by applying an inverse normal scores transformation; the scores were ranked, ranks were transformed into quantiles and quantiles were converted to normal deviates. As only fasting and 2 hour OGTT data were available for the FUSION participants, we could not calculate the incretin effect in this sample.

In the Botnia study, the first phase insulin secretion and AIR were calculated from the first 10 min during an IVGTT in 488 nondiabetic participants and analysis was performed by linear regression adjusted for age, sex and BMI. The percent incretin effect was estimated in a subset of 351 individuals from Botnia who underwent both an OGTT and an IVGTT using the formula: 100% × (AUCins OGTT-AUCins IVGTT)/AUCins OGTT[16]. AUCs were adjusted for age and sex, and analyses were performed with or without BMI adjustment.

In the Denmark study, association of *GIPR* rs10423928 was assessed with AIR during IVGTT and with an estimate of the incretin effect in 198 nondiabetic offspring and spouses of individuals with type 2 diabetes. AIR was calculated as the incremental area under the serum insulin curve during the first 10 min after intravenous glucose administration using the trapezoidal method. The incretin effect was calculated as described previously[16,35].

The incremental AUC of IVGTT s-insulin curve was calculated from 0 to 19 min (measurements at 0, 2, 3, 4, 5, 6, 7, 8, 10, 12, 14, 16 and 19 min) because intravenous tolbutamide was given at 20 min. The incremental s-insulin AUC during OGTT was calculated from 0 to 120 min (measurements at 0, 10, 20, 30, 40, 50, 60, 75, 90, 105 and 120 min). Effect size and P values were calculated by a mixed linear model assuming an additive model adjusted for family, age and sex or family, age, sex and BMI. AIR was log-transformed before analysis.

In the EUGENE2-Kuopio study, data from an IVGTT, OGTT, and genotypes for *GIPR* rs10423928 were available from 262 nondiabetic offspring of individuals with type 2 diabetes from the Kuopio center of the EUGENE2 study. Insulin secretion was assessed as the first-phase insulin release during

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IVGTT, computed as the incremental area under the insulin curve (AUC) for the first 10 min. First-phase insulin release was tested for association with rs10423928 using a mixed linear model (SPSS 14.0) in order to account for relatedness among individuals. Models were adjusted for sex, age, age^2, familial relationship and BMI. Effect sizes per minor allele of the *GIPR* rs10423928 are reported.

URLs. FastSNP, http://fastsnp.ibms.sinica.edu.tw; METAL, http://www.sph.umich.edu/csg/abecasis/Metal/index.html; MACH, http://www.sph.umich.edu/csg/abecasis/mach/; IMPUTE, http://mathgen.stats.ox.ac.uk/impute/impute.html.

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