SUPPLEMENTARY INFORMATION

Variants in the melatonin receptor 1B gene (*MTNR1B*) influence fasting glucose levels

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Supplementary Note

Study samples for continuous traits

The four consortia that are represented within the present MAGIC analysis are : (i) ENGAGE, featuring a meta-analysis of the deCODE, Northern Finland Birth Cohort 1966 (NFBC1966), Netherlands Twins Register/NEtherlands Study of Depression and Anxiety (NTR/NESDA), and Rotterdam Study GWA scans; (ii) GEM, including a meta-analysis of the Lausanne (CoLaus) and TwinsUK scans; (iii) DFS, involving the Diabetes Genetics Initiative (DGI), Finland-United States Investigation of NIDDM Genetics (FUSION) and SardiNIA scans, and (iv) the Framingham Heart Study. Study samples constitute a total of 36,610 individuals of European ancestry. Detailed information on each of these studies is provided in **Supplementary Table 1**. This table summarizes the clinical characteristics of the subjects studied and operational details of each of the ten GWAS (including genotyping platforms, quality control filters for individuals and SNPs, and imputation and data analysis methods). Indices of beta-cell function (HOMA-B) and insulin sensitivity (HOMA-IR) were derived from paired fasting glucose and insulin measures using the homeostatic model assessment, see **Supplementary Table 1.**

Study samples for T2D case-control studies

In addition to the primary meta-analysis targeted at identifying variants influencing fasting glucose, we examined the most promising signals for their relationship to T2D using available GWA data gathered from 13 case-control studies involving a total of 18,236 T2D cases and 64,453 controls. Many of these studies – WTCCC-T2D, DGI, FUSION, DeCODE, KORA, CCC (the Cambridgeshire Case-Control Study), ADDITION/ELY, NORFOLK (The Norfolk Diabetes Case-Control Study), METSIM, FUSION stage 2 – have been described extensively in previous publications[1-8]. Additional samples include:

Rotterdam: This sample included 1178 T2D cases and 4761 controls ascertained from the Rotterdam study[9,] a prospective cohort study initiated in 1990 in Ommoord, a suburb of Rotterdam, among 10,994 men and women

aged 55 and over. Baseline measurements were obtained between 1990 and 1993 and participants were subsequently examined every 2-3 years. For the T2D case-control comparison, cases were those with T2D present at baseline (prevalent cases, n=631) or on follow-up (n=547). Diabetes was defined by physician diagnosis, use of anti-diabetic medication and/or standard diagnostic glucose measurements[10.] The remaining individuals with GWA data and no diagnosis of diabetes served as the controls.

UK Type 2 Diabetes Genetics Consortium collection and OxGN/58BC: these samples represent an expansion of the "UK Stage 2" samples described in ref 8. The UKT2DGC ("Dundee") collection study sample of 4124 T2D cases and 5111 controls includes subjects previously described (in ref 1) as RS1 and RS3, together with a third tranche of cases and controls ("RS4") ascertained more recently. Since all three tranches were ascertained using precisely the same scheme, these are here combined into a single sample. All cases and controls were of European White descent, living in the Tayside region of Dundee when recruited. Cases had T2D diagnosed between the ages of 35-70 years (inclusive). The diagnosis of diabetes was based on either current prescribed treatment with diabetes-specific medication or, in the case of individuals treated with diet alone, laboratory evidence of hyperglycemia as defined by the World Health Organization. Patients were excluded if they had an established (clinical and/or molecular) diagnosis of monogenic diabetes (e.g. maturity-onset diabetes of the young, mitochondrial diabetes) or if they had been treated with regular insulin therapy within 1 year of diagnosis. Controls were from the same population base, aged below 80 years and had not been diagnosed with diabetes at the time of recruitment (or subsequently). Control subjects were excluded from analysis if laboratory investigations at the time of recruitment provided evidence of hyperglycemia (fasting glucose >7.0 mmol/l, HbA1c >6.4%). The OxGN sample (equivalent to RS2 from previous papers[1,10]) includes 335 T2D cases, and was matched to additional controls from the 1958 Birth Cohort (non-overlapping with those included in the 1500 cohort members studied in the WTCCC).

T2D case-control genotyping

Genotyping for CCC, ADDITION/ELY and Norfolk samples was performed at the MRC Epidemiology Unit Research Laboratory using custom TaqMan® SNP assay (Applied Biosystems, Warrington, UK), with 10ng of genomic DNA. The call frequency of genotyped samples was >96% and HWE p-values >0.20. Between 2-4% duplicate samples were used per study and these were all 100% concordant. Associations between each SNP and diabetes were tested in these samples using logistic regression analyses, assuming an additive genetic model and adjusting for age and sex.

Genotyping of rs10830963 in the UKT2DGC, OxGN and 58BC samples was performed at the Oxford Centre for Diabetes, Endocrinology and Metabolism (OCDEM) using Applied Biosystems designed assays based on modified TaqMan assays, details of which are available on their website (https://products.appliedbiosystems.com/). Assays were validated prior to use, using a standard 96-well validation plate. Genotype call frequency rates exceeded 97% in the replication sets. Tests for association with T2D were performed using logistic regression with adjustment for

sex and age. Genotyping of rs10830963 in FUSION Stage 2 (98.0% success) and METSIM (97.4% success) used Sequenom iPLEX Gold SBE assays and was carried out at the National Human Genome Research Institute (NHGRI). FUSION Stage 2 samples were analyzed using logistic regression with adjustment for sex, 5-year age category and birth province and an additive model for the genetic effect. METSIM samples were analyzed using logistic regression with adjustment for 5-year age category and an additive model for the genetic effect.

Statistical analysis

Genome-wide Meta-analysis: GWA scans informative for FG were first analysed by the four component consortia (ENGAGE, GEM, DFS and Framingham). Details of imputation and meta-analysis approaches are described in S**upplementary Table 1.** Each group then used an informal approach – based on the strength of the evidence for association observed for FG and related traits, combined with some assessment of biological candidacy – to identify a list of between 10 and 20 FG signals for exchange with the other three groups. Signals showing consistent evidence for association across studies were targeted for further studies.

Regional Meta-analysis: A weighted, z-score based, fixed-effects, meta-analysis method was used to combine FG association results for genotyped and imputed SNPs in 1Mb regions flanking index SNPs showing consistent evidence of association across all ten studies. These meta-analyses were implemented in METAL; www.sph.umich.edu/csg/abecasis/metal/: details are included in **Supplementary Table 1** as are descriptions of study-specific outcome transformations and model adjustments. For each SNP, the *P* value was converted to a z-statistic signed to reflect the direction of association given a reference allele. Each z-score was then weighted such that each sample-specific weight was proportional to the square root of number of individuals in the sample. Weighted z-statistics were summed across the studies and the summary z-score was converted to a two-sided *P* value. This method was used to derive estimates of statistical significance (additive genetic model, 1-df trend test) across all ten studies for FG (unadjusted and conditional analyses), fasting insulin, HOMA-B and HOMA-IR. The derivation of unified estimates of effect-size (particularly for insulin and derived HOMA measures) is complicated by the use of incompatible study-specific transformations and covariate inclusions within individual studies. In the case of FG, additive effect sizes for each SNP were then calculated using standard formulas that took allele frequency and the mean FG level for each genotype into account[11]. For SNPs, such as rs10830963, which was imputed in most of the study samples included, we based FG level estimation of the most probable genotype for every individual.

Conditional analysis: Each study carried out regional association analysis with FG simultaneously including all three lead SNPs (rs10830963, rs560887 and rs4607517) as covariates (along with age, gender and study-specific covariates) to detect secondary independent signals at any of the three loci. Inclusion of all three SNPs in the model is expected to explain more residual variance than adjustment for only the lead SNP at each locus, and thus should result in increased power to detect additional effects. Meta-analysis across the ten studies was performed and compared to results obtained before adjustment to identify additional independent association signals. No

independent signals of association with genome-wide significant evidence of association in meta-analysis (P<5 x 10^{-7}) were identified at the three loci. In addition, to examine the possible effects of BMI on the strength of FG association, each study performed linear regression analysis before and after adjustment for BMI, in addition to adjusting for study-specific covariates, age and gender. Results were meta-analysed as described above.

Type 2 diabetes meta-analysis: The summary statistics (odds ratios and 95% confidence intervals) for each of the separate studies were combined in meta-analysis using the inverse variance fixed effects model. The DGI GWAs includes a discordant sibship component, which was incorporated into the overall significance test using the weighted z-score method as described above. However, the OR estimate for the DGI study does not incorporate the sibship component, as the methodology for this has not been developed[2].

Supplementary Methods References

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Detailed Acknowledgements

GEM

The work of the GEM consortium and the salaries of the authors affiliated to the Wellcome Trust Sanger Institute are supported via the Wellcome Trust. NS is also funded through the European Union Sixth Framework Program (LSHM-CT-2006-037197) and IB and EW are supported in part by LSHM-CT-2003-503041. The **CoLaus** study was

supported by research grants from GlaxoSmithKline and the Faculty of Biology and Medicine of Lausanne, Switzerland. The authors express their gratitude to the participants in the Lausanne CoLaus study, to the investigators who have contributed to the recruitment, in particular Yolande Barreau, Anne-Lise Bastian, Binasa Ramic, Martine Moranville, Martine Baumer, Marcy Sagette, Jeanne Ecoffey and Sylvie Mermoud for data collection and to Allen Roses, Paul Matthews, Dan Burns, Eric Lai and Lefkos T. Middleton for their support and Dan Burns and Eric Lai at GSK for genotyping. Some computation was carried out on the Vital-IT system at the Swiss Institute of Bioinformatics. The **TwinsUK** study was funded by the Wellcome Trust, European Commission (QLK6-CT-2002-02629, GENOMOS, GEFOS), NWO Investments (175.010.2005.011), the European Union FP-5 GenomEUtwin Project (QLG2-CT-2002-01254) and supported by the Department of Health via the NIHR comprehensive Biomedical Research Centre award to Guys and St. Thomas' NHS Foundation Trust in partnership with Kings College London. The authors thank study participants and staff from the TwinsUK studies, in particular Irina Gillham-Nasenya and Rami Swaminathan; staff of the DNA Collections and Genotyping Facilities at the Wellcome Trust Sanger Institute for sample preparation, genotyping and quality control, including Vasudev Kumanduri, Rhian Gwilliam, Pam Whittaker, Radhi Ravindrarajah, Douglas Simpkin and Cliff Hinds. Genotyping was provided by Le Centre National de Génotypage, France, led by Mark Lathrop; Duke University, North Carolina, USA, led by David Goldstein; and the Finnish Institute of Molecular Medicine, Finnish Genome Center, University of Helsinki, led by Aarno Palotie.

ENGAGE

The work of the ENGAGE (European Network for Genetic and Genomic Epidemiology) Consortium is funded through the European Community's Seventh Framework Programme (HEALTH-F4-2007- 201413).

The collection and characterization of the **Northern Finland Birth Cohort** has been supported by the Academy of Finland (104781), MRC (G0500539), and the Wellcome Trust (Project Grant GR069224). Genotyping and analysis was performed at the Broad Institute through funding from the NHLBI under the STAMPEED initiative (1-R01-HL087679-01). MK is funded by the European Bioinformatics Institute and by Framework 6 program MolPAGE (LSHG-CT-2004-512066). The NFBC group would like to acknowledge the contributions of the investigators in Oulu (particularly Aimo Ruokonen, Anna-Liisa Hartikainen, Hannu Martikainen), of Stacey Gabriel and her team at the Broad, and especially Mark Daly (Broad institute), Chiara Sabetti and Susan Service (UCLA) and Samuli Ripatti and Juha Muilu (University of Helsinki) for their primary analysis and informatics support for the GWA data. Thanks are also due to the other informaticians involved in the ENGAGE project from Karolinska (Jan-Eric Litton), Riga and EBI. The **Rotterdam Study** is supported by the Erasmus Medical Center and Erasmus University Rotterdam, the Netherlands Organization for Scientific Research (NWO), the Netherlands Organization for Health Research and Development (ZonMw), the Research Institute for Diseases in the Elderly (RIDE), the Ministry of Education, Culture and Science, the Ministry of Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam. The GWA analysis is supported by the NWO-Groot grant. The Rotterdam study thanks Pascal Arp

and Mila Jhamai for genotyping, and Dr Fernand Rivadeneira and Dr Michael Moorhouse for data management and support with analysis. **NTR and NESDA** would like to acknowledge support from NWO including (a) genetic basis of anxiety and depression (904-61-090); (b) resolving cause and effect in the association between exercise and well-being (904-61-193); (c) twin family database for behavior genomics studies (480-04-004); (d) twin research focusing on behavior (400-05-717) and (e) Center for Medical Systems Biology (NWOGenomics). Additional support comes from Spinozapremie (SPI 56-464-14192); the Centre for Neurogenomics and Cognitive Research (CNCR-VU); the European Union (QLRT-2001-01254); NIMH (R01 MH059160); and the Geestkracht program of ZonMW (10-000-1002) as well as matching funds from universities and mental health care institutes involved in NESDA (GGZ Buitenamstel-Geestgronden, Rivierduinen, University Medical Center Groningen, GGZ Lentis, GGZ Friesland, GGZ Drenthe). Major funding for the GWA genotyping was provided by the Foundation for the US National Institutes of Health via the Genetic Association Information Network (GAIN) initiative. We would like to acknowledge the contribution of Patrick Sullivan (Principal Investigator of the GAIN_MDD project). **DeCODE** would like to thank the individuals with T2D and other study participants whose contribution made this work possible. DeCODE also thank the nurses at Noatun (deCODE's sample recruitment center) and personnel at the deCODE core facilities for their hard work and enthusiasm. **WTCCC T2D case-control data** were generated using case samples recruited through funding from Diabetes UK, British Diabetic Association Research, and the UK Medical Research Council (Biomedical Collections Strategic Grant G0000649): genotyping was performed at Affymetrix, supported by the Wellcome Trust: we acknowledge the important contribution of our colleagues within the Case Control Consortium particularly Peter Donnelly, Jonathan Marchini (Oxford), Andrew Hattersley, Tim Frayling and Michael Weedon (Exeter). The research was also supported by the Oxford NIHR Biomedical Research Centre. **KORA** acknowledges Christian Gieger and Guido Fischer for expert data handling. Kora thanks Klaus Strassburger and Guido Giani for expert statistical advice. The MONICA/KORA Augsburg studies were financed by the GSF-National Research Center for Environment and Health, Neuherberg, Germany and supported by grants from the German Federal Ministry of Education and Research (BMBF), the German Diabetes Center was supported by the German Federal Ministry of Health and Social Security and the Ministry of Science and Research of the State North-Rhine Westphalia. Part of this work was financed by the German National Genome Research Network (NGFN). KORA research was also supported within the Munich Center of Health Sciences (MC Health) as part of LMUinnovativ. KORA thanks all members of field staffs who were involved in the planning and conduct of the MONICA/KORA Augsburg studies.

DGI-FUSION-SardiNIA

The Diabetes Genetics Initiative (DGI) thanks study participants, the Botnia and Skara research teams for clinical contributions, and colleagues at MGH, Broad, Novartis and Lund for data collection, genotyping and analysis. The initial GWAS genotyping was supported by Novartis (to DA). DA was a Burroughs Wellcome Fund Clinical Scholar in Translational Research, and is a Distinguished Clinical Scholar of the Doris Duke Charitable Foundation. LG, TT, BI

and the Botnia Study are principally supported by the Sigrid Juselius Foundation, the Finnish Diabetes Research Foundation, The Folkhalsan Research Foundation and Clinical Research Institute HUCH Ltd; work in Malmö, Sweden was also funded by a Linné grant from the Swedish Research Council (349-2006-237). **FUSION** would like to thank the many Finnish volunteers who generously participated in this study as well as colleagues Cristen J. Willer, Timo T. Valle, William L. Duren, Amy J. Swift, Peter S. Chines, Narisu Narisu, Andrew G. Sprau, and Li Qin for data collection and analysis, informatics, and genotyping support. The Center for Inherited Disease Research supported the FUSION GWA genotyping. Support for this study was provided by the following: American Diabetes Association grant 1-05-RA-140 (R.M.W.) and NIH grants DK069922 (R.M.W.), U54 DA021519 (R.M.W.), DK062370 (M.B.), and DK072193 (K.L.M.). Additional support comes from the National Human Genome Research Institute intramural project number 1 Z01 HG000024 (F.S.C.). **SardiNIA** would like to thank the Sardinian volunteers who generously supported the study and made it possible as well as G. Albai, G. Usala, M. Dei, S. Lai, A. Maschio, F. Busonero, A. Mulas for data collection and genotyping support. This research was supported in part by intramural research funds from the National Institute on Aging and by research grants from the National Institutes of Health (NHLBI, NHGRI to GRA) including HG-02651 and HL-084729. We also acknowledge the support of the administration of Lanusei, Ilbono, Arzana and Elini (Sardinia, Italy).

Framingham

The work of the Framingham group is supported by the National Heart, Lung, and Blood Institute's Framingham Heart Study (Contract No. N01-HC-25195), National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK) R01 DK078616 to Drs. Meigs, Dupuis and Florez, NIDDK K24 DK080140 to Dr. Meigs, NIDDK Research Career Award K23 DK065978 to Dr. Florez, and the Boston University Linux Cluster for Genetic Analysis (LinGA) funded by the NIH NCRR Shared Instrumentation grant (1S10RR163736-01A1), and the Framingham SNP Health Association Resource (SHARe) study.

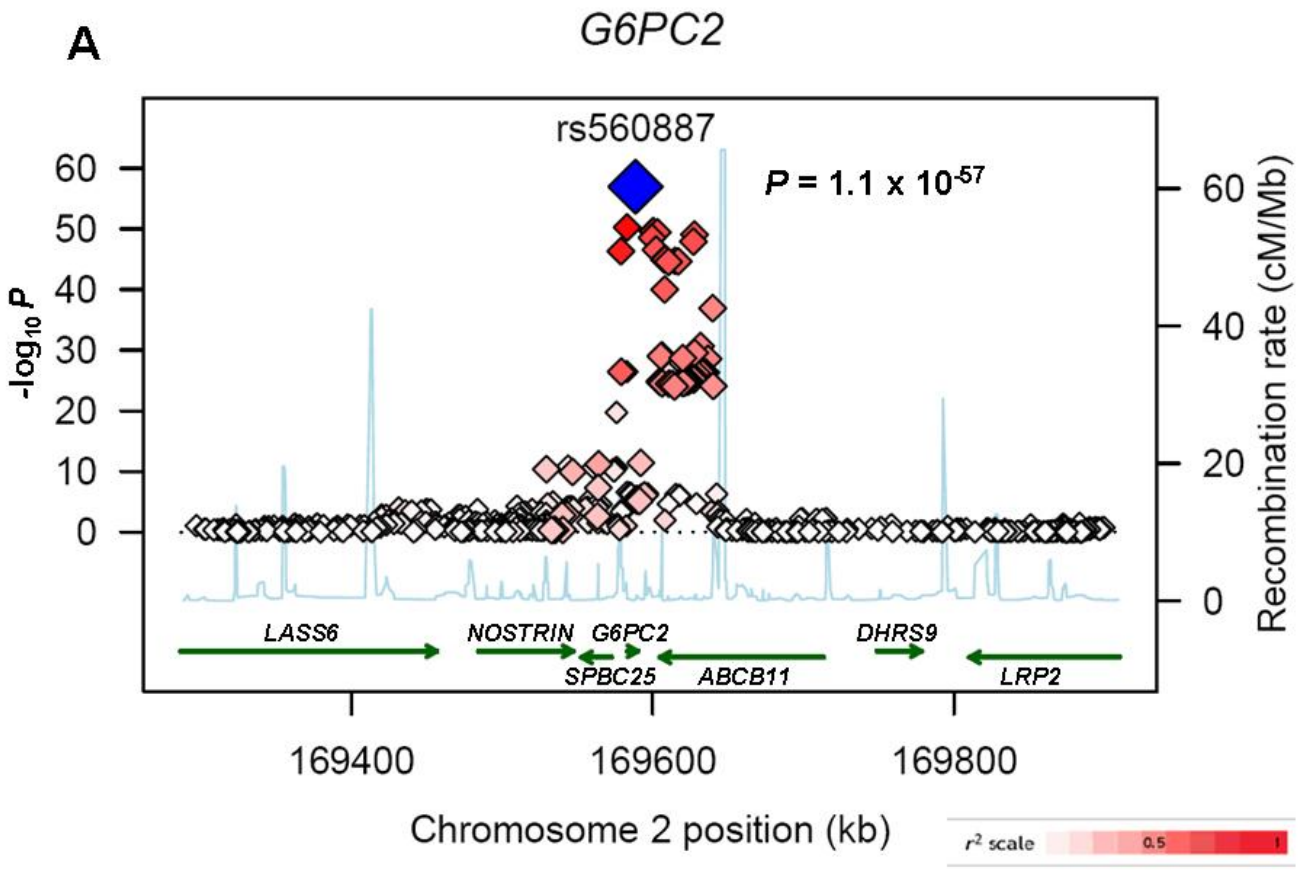
Additional T2D case-control data

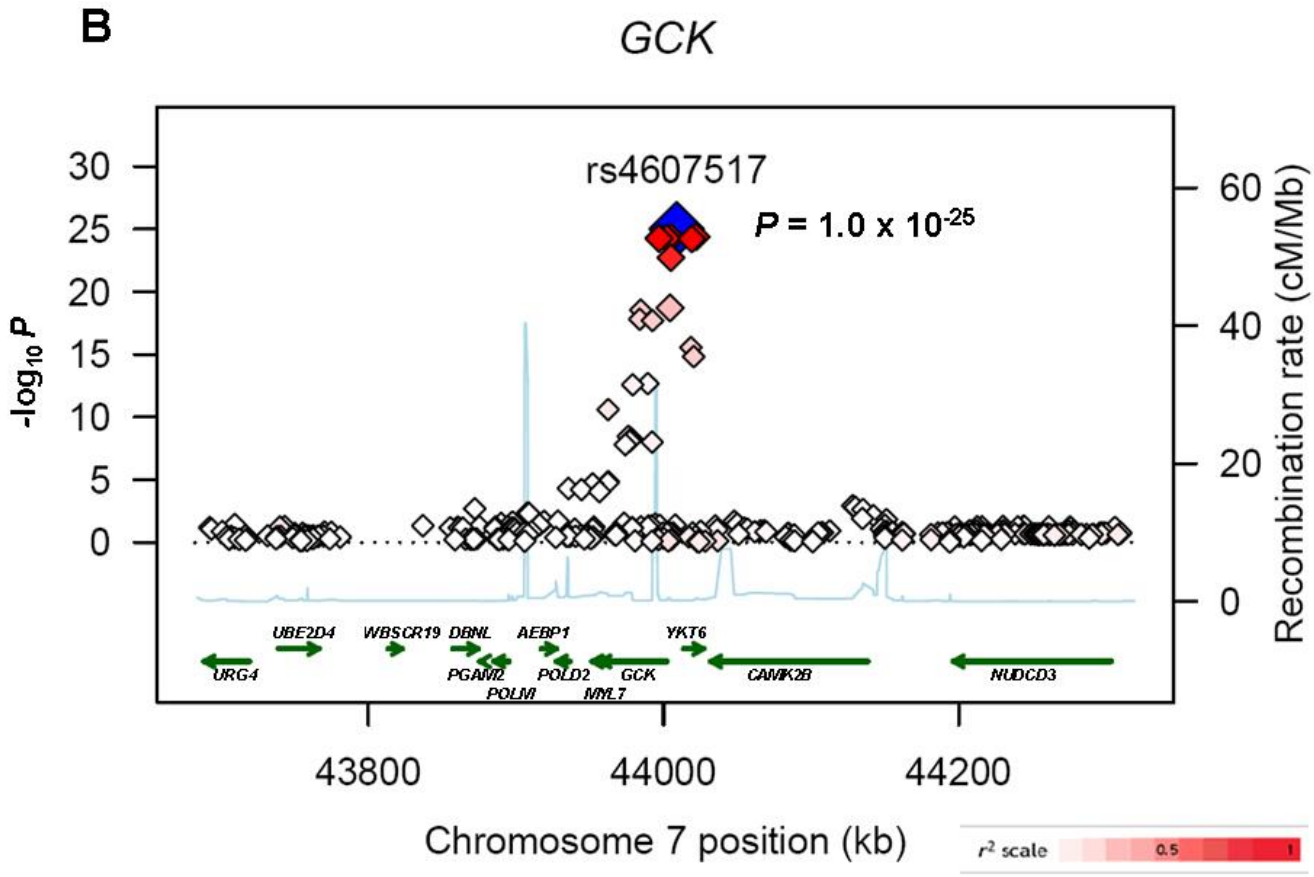
CCC/ADDITION/ELY/NORFOLK/BOB: The work on the Cambridgeshire case-control, Ely, ADDITION and EPIC-Norfolk studies was funded by the Wellcome Trust and MRC. The Norfolk Diabetes study is funded by the MRC with support from NHS Research & Development and the Wellcome Trust. We are grateful to Dr Simon Griffin, MRC Epidemiology Unit, for assistance with the ADDITION study and Professor Mike Sampson and Dr Elizabeth Young for help with the Norfolk Diabetes Study. We thank the technical team at the MRC Epidemiology laboratory for genotyping and informatics support.

UKT2DGC: The UK Type 2 Diabetes Genetics Consortium collection was supported by the Wellcome Trust (Biomedical Collections Grant GR072960). Genotyping of the UKT2DGC and OxGN/58BC samples was supported by the European Commission (EURODIA LSHG-CT-2004- 518153), MRC (Project Grant G016121) and Diabetes UK.

METSIM: Markku Laakso is supported by the Academy of Finland grant 124243.

Supplementary Figure 1: Regional plots of confirmed fasting glucose associations across MAGIC GWAS (10 studies) for the (A) *G6PC2* and (B) *GCK* regions. Meta-analysis -$\log_{10}$ *P*-values are plotted as a function of genomic position (NCBI Build 35). In each panel, the SNP with the strongest signal is denoted by a blue diamond. Estimated recombination rates (from HapMap) are plotted to reflect the local linkage disequilibrium structure around associated SNPs and proxies (according to a white-to-red scale from r^2=0 to r^2=1; based on pair-wise r^2 values from HapMap CEU). Gene annotations were taken from the University of California-Santa Cruz genome browser.




B
GCK
rs4607517
P = 1.0 x 10-25
-log10 P
Recombination rate (cM/Mb)
30
25
20
15
10
5
0
60
40
20
0
UBE2D4
WBSCR19
DBNL
AEBP1
YKT6
URG4
PGAM2
POLD2
GCK
CAMK2B
NUDCD3
POLM
MYL7
43800
44000
44200
Chromosome 7 position (kb)
r2 scale
0.5
1

Supplementary Table 1. **Sample characteristics and details of analysis metrics and methods for all cohorts included in the study.**

	Population-based samples								Case-control samples	
STUDY SAMPLE	**TwinsUK**	**CoLaus**	**SardiNIA**	**Framingham**	**NTR/NESDA**	**NFBC1966**	**deCODE**	**Rotterdam Study**	**FUSION**	**DGI**
GLUCOSE MEASURE-MENTS										
Sample	Fasting plasma	Fasting venous plasma	Fasting blood	Fasting plasma	Fasting plasma	Fasting blood	Fasting plasma	Fasting plasma	Fasting plasma	Fasting plasma and blood
Collection method	10 hr overnight fast. Sodium Fluoride tube is used, 2 ml grey top tube, blood being sent within 30min from collection for analyses. Blood is centrifuged to get plasma. Plasma is then used for the Glucose test.	Overnight fast	Overnight fast	≥8 hr overnight fast	Overnight fast, glucose measured or samples snapfrozen within 5 hr of collection	Blood collected between 0800 and 1100 h. Sample mixed with EDTA anticoagulant and precipitated with 0.5ml of perchloric acid	Overnight fast	Serum separated by centrifugation and quickly frozen in liquid nitrogen	Overnight fast and plasma collected in EDTA tubes	Conversion factor of 1.13 to plasma glucose concentrations applied to blood glucose concentrations
Assay	Enzymatic colorimetric slide assay (Johnson and Johnson, UK) and automated analyzers	Glucose dehydrogenase assays (Roche Diagnostics, CH)	Hexokinase/ glucose-6-phosphate hydrogenase kit (Bayer Healthcare)	Hexokinase reagent kit (a-gent glucose test, Abbott, South Pasadena, California)	Vitros 250 glucose assay (Johnson & Johnson, Rochester, USA)	Glucose dehydrogenase method (granutest 250, Diagnostica Merck, Darmstadt, Germany)	Roche diagnostics and Technicon auto-analyzer or the Hitachi 912 clinical chemistry auto-analyser	Glucose hexokinase method	Glucose oxidase method (Yellow Springs instruments, Yellow Springs, OH and autoanalyser) and hexokinase method	Glucose oxidase method (Beckman Glucose Analyzer, Beckman Instruments, Fullerton, CA)[1]
Reference	[2]	[3]		[4]		[5]		[6]		

STUDY SAMPLE	TwinsUK	CoLaus	SardiNIA	Framingham	NTR/NESDA	NFBC1966	deCODE	Rotterdam Study	FUSION	DGI
SAMPLES										
EXCLUSIONS	Self-reported diabetes	Self-reported diabetes	Diabetes ascertained by medical record review	Non-fasting individuals, Type 1 diabetes, Other diabetic treatment, Fasting glucose ≥ 7 mmol/L	Pregnant women, Non-fasting individuals, Type 1 diabetes, Outliers ±3SD of distribution either Fasting Glucose/Fasting Insulin	Pregnant women, Non-fasting individuals, Type 1 diabetes, Other diabetic treatment, Outliers ±3SD of distribution either Fasting Glucose/Fasting Insulin	Non-fasting individuals, Type 1 diabetes, Other diabetic treatment, Outliers ±3SD of distribution either Fasting Glucose/Fasting Insulin	Non-fasting individuals, Type 1 diabetes, Other diabetic treatment, Outliers ±3SD of distribution either Fasting Glucose/Fasting Insulin	Diabetes ascertained by OGTT, medical record review or GAD Ab positivity; diabetes medication	Diabetes ascertained by OGTT, medical record review or GAD Ab positivity
Samples with phenotype: N all (%males/ %females)	1,828 (0/100)	5,000 (46/54)	4,305 (43.8/56.2)	6,479 (46.0/54.0)	3,166 (33.3/66.7)	4,245 (49.3/50.7)	6,240 (44.4/55.6)	2,058 (43/57)	1,233 (50/50)	1,455 (48.5/51.5)
Age [Mean (sd) males / Mean (sd) females], years	-(-)/ 50.16 (12.97)	52.46 (10.72)/ 53.84 (10.73)	44.08 (18.10) / 43.19 (17.3)	45.9 (11.5) / 46.0 (11.6)	46.1 (13.4) / 42.3 (13.2)	31 (-)/ 31 (-)	64.3 (16.0) / 59.1 (18.2)	63.8(5.5) / 64.2 (6.1)	60.05 (11.53) / 61.16 (10.89)	58.22 (10.13)/ 59.08 (9.98)
BMI [Mean (sd) males / Mean (sd) females], kg/m2	-(-)/ 25.4 (4.74)	26.36 (3.84)/ 24.94 (4.63)	26.15 (4.11) / 24.75 (5.03)	27.7 (4.2) / 25.9 (5.5)	25.9 (3.8) / 25.0 (4.7)	25.13 (3.51) / 23.89 (4.18)	27.9 (4.5) / 28.3 (6.0)	25.9 (2.8) / 26.3 (3.8)	26.98 (3.56) / 27.07 (4.28)	26.63 (3.23) / 26.76 (4.18)
Fasting glucose* [Mean (sd) males / Mean (sd) females], mmol/l	-(-)/ 4.63 (0.63)	5.62 (0.83)/ 5.25 (0.66)	5.22 (1.41) / 4.83 (1.11)	5.35 (0.45) / 5.06 (0.47)	5.4 (0.6) / 5.2 (0.6)	5.17(0.56) / 4.91(0.46)	5.51 (0.75) / 5.2 (0.67)	5.74(0.86) / 5.61(0.86)	5.44 (0.45) / 5.19 (0.47)	5.33 (0.56) / 5.29 (0.52)

*Mean fasting glucose concentration is reported for fasting blood or plasma glucose, respectively for each study, as it is reported at the beginning of the table

STUDY SAMPLE	TwinsUK	CoLaus	SardiNIA	Framingham	NTR/NESDA	NFBC1966	deCODE	Rotterdam Study	FUSION	DGI
GENOTYPING										
Genotyping platform & SNP panel	Illumina HumanHap300 v2	Affymetrix 500K Array Set	Affymetrix 500K Array Set	Affymetrix 500K and MIPS 50K	Perlegen 600K	Illumina HumanCNV-370DUO Analysis BeadChip	Human Hap300 and Human Hap300-duo+ Bead Arrays, Illumina	Version 3 Illumina Infinium II HumanHap550	Illumina HumanHap300, also 1536 T2D candidate gene SNPs	Affymetrix 500K SNP array
Genotyping centre	WTSI	-	SardiNIA Research Laboratory, Lanusei, Italy	Affymetrix	Perlegen / GAIN	Broad Institute	deCode Genetics	Erasmus MC Rotterdam	Center for Inherited Disease Research	Broad Institute, Cambridge, MA, USA
Genotyping calling algorithm	Illuminus	BRLMM	BRLMM	BRLMM	Perlegen's proprietary genotype calling algorithm	Beadstudio	Beadstudio	Beadstudio	Beadstudio	-

STUDY SAMPLE	TwinsUK	CoLaus	SardiNIA	Framingham	NTR/NESDA	NFBC1966	deCODE	Rotterdam Study	FUSION	DGI
SAMPLE QC										
Call rate [filter detail / N individuals excluded]	95% / 130	≥ 90% / 379	>95% / none	97% / 119	99.2% / 8	≥95% / 472	>95% / 80	≥97.5% / 209	>97.5% / 7	>95% /none
Heterozygosity [filter detail / N individuals excluded]	<33% and >37% /46	n.a.	n.a.	5 SD from mean (< 25.758% or > 29.958%) / 16	None		None	FDR<0.01 / 14	None	None
Ethnic outliers excluded	4	n.a.	n.a.	None	None	None	None	3	None	None
Other exclusions	Duplicate concordance <99% / -	1) Gender inconsistency with genetic data from X-linked markers; 2) Inconsistent genotypes when compared with control markers; 3) Duplicates and first and second degree relatives	Verified sex using X-linked markers; verified relationships and checked for duplicates using RELPAIR	> 1000 Mendelian errors / 1	Contaminated samples : < 0.74 IBS / 1 individual out, Relatedness : IBS > 828, 38 individuals out, clustering as second or first degree relatives. Gender mismatch= 2 individuals, due to chromosomal deviations	Duplicates concordance with another DNA >0.99 / 2 Contaminated samples: IBS pairwise with most other samples>0.99= 3 IBS pairwise sharing >0.20 / 53, Withdrew consent= 14, Gender mismatch: genotypic gender different from phenotypic / 15.	None	Duplicates: IBS>.95 (excluded: 130), Gender mismatch: X/Y checks (also XXY excluded) (excluded: 4)	None	Parent-offspring combinations
Individuals for analysis	2,224	5,000	4,305	6,479	3,063	4,762	6,240	5,974	1,233	1,455
SNP QC (prior					.					

to imputation)										
MAF [filter detail / N SNPs excluded]	1% / 9,489	-	5% / 130,382	1% / 68,953	1% / 41,526	1% / 7,553	1%	1%	1%	1% / 66,549
HWE [filter detail / N SNPs excluded]	10^{-6} / 1555	> 10^{-7} / 35,417	10^{-6} / 7,842	10^{-6} / 20999	10^{-4} / 57726	10^{-4} / 3,282	10^{-4}	10^{-6}	10^{-6}	10^{-6} / 5,775
Call rate [filter detail / N SNPs excluded]	95% / 777	≥ 70% 157	>90% / 3,975	95% / 23312	> 95%, > 99% (MAF) < 0.05 / 161,149	≥95% / 6,712 ≥99% (MAF<5%) / 672	≥95% ; ≥99% (MAF<5%)	98%	>=90%	>95% / 34,761
Other			Mendel errors > 2 / 2,010		Mendel errors > 2/ 536; Duplicate errors > 2 / 1143				NMI + duplicate pair discrepancies > 3	Other SNP exclusions (3605 SNPs that map to multiple locations)
SNP number in QC'd dataset	307,040	390,631	356,359	378,163	425,052	328,007	299,319	486,261	304,581	389,878
IMPUTATION STATS										
Imputation software	IMPUTE	IMPUTE (v0.2.0)	MACH/MERLIN	MACH	None	IMPUTE	IMPUTE	MACH	MACH 1	MACH
Imputation quality metrics	Post prob on individual genotype calls ≥ 0.9	Proper-info ≥ 0.40	r2hat > 0.3	r2hat > 0.3	None	Proper-info > 0.4	Proper-info > 0.4	Not filtered, all analysed	r2hat>0.3	r2hat>0.3
Other SNP QC filters applied?	Best guess genotypes used for study; MAF ≥ 1%	MAF ≥ 1%	NMI inconsistencies >= 5	MAF ≥ 1%	None	MAF > 1%	MAF > 1%	MAF > 1%		Best guess genotypes used for study

STUDY SAMPLE	TwinsUK	CoLaus	SardiNIA	Framingham	NTR/NESDA	NFBC1966	deCODE	Rotterdam Study	FUSION	DGI
DATA ANALYSIS										
Number of SNPs in analysis N imputed	2,434,545	2,557,249	2,252,558	2,540,223	425,052 (genotyped)	2,378,857	Genotyped 299,319 (imputed SNPs in 3 studied regions 2.385)	2,543,887	2,556,824	2,411,071
Trait transformation	Natural logarithm	Standardized, log10 transformed	Quantile normalization	Residuals	Natural logarithm	Natural logarithm	Natural log	Z-scaling of residuals of log-transformed trait	Inverse normalization of residuals	none
Adjustments	Age	Gender, age	BMI, age, age^2, sex	Gender specific residuals adjusted for age and age^2	Gender, age	Gender, 3 PCs based on GW data determining geographical differences	Gender, age	Gender, age	Age, age2, gender, birth province, study	Age, gender, log BMI, clinical site
Analysis method	Score test (FastAssoc)	Linear regression (additive model)	Score test (FastAssoc)	Linear Mixed Effect models	Regression, additive model, Wald test	Cochrane-Armitage test for additive genetic effect	Test for additive genetic effect	ML regression	Linear regression	Linear regression
Software for analysis	MERLIN	SNPtest	MERLIN	LMEKIN (R package)	Plink	SNPTEST	R / SNPTEST	ProbABEL	Merlin	PLINK
Genomic Control Lambda	1.002	1.009	1.061	1.013	1.014	1.017	1.094	n.a.	1.008	1.044
REFERENCES										
Reference cohort	7	3	8	9-11	12	13		14,15	16	1,17
Reference GWAS	18	19	20		12	-	21		16	1
Website	www.twinsuk.ac.uk		http://sardinia.nia.nih.gov	http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000007.v2.p1	http://www.tweelingenregister.org/; http://www.nesda.nl	kelo.oulu.fi/NFBC	www.decode.is	http://www.epib.nl/ergo.htm, http://ict.nwo.nl/projecten.nsf/pages/2300132533	http://fusion.sph.umich.edu	www.broad.mit.edu/diabetes

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Supplementary Table 2: List of SNPs showing fasting glucose associations exchanged between the four consortia (ENGAGE, DFS, GEM, FHS).

P-values are reported for the 10 to 20 SNPs exchanged between groups based on individual, interim, meta-analyses of the evidence for association with FG (n=6,479-12,389). The significance levels reported here will differ from the final analysis within each consortium (as reported elsewhere in this manuscript), depending on the completeness of individual data from participating studies at the time of these interim analyses.

The ENGAGE analysis reported here involved data from three studies (NFBC1966, Rotterdam and DeCODE, but not NTR/NESDA as this was not available at the time of exchange). SNPs selected were representative of signals that attained a meta-analysis *P*- value<10^{-5} with inclusion of some additional SNPs with less marked signals but mapping to biological candidates. The GEM analysis was based on data from CoLaus and TwinsUK and SNPs were selected for exchange based on a meta-analysis *P*-value <10^{-5}. The DFS signals used data from DGI, FUSION and SardiNIA, and SNPs were selected based on a meta-analysis *P*-value <10^{-5}, complemented by one biological candidate (rs12682508) with modest associations to multiple glycemic traits: two SNPs were selected at *GCK* and *G6PC2*. Finally, FHS exchanged the SNPs representing signals with the strongest association analysis P-value, plus additional signals with more modest FG associations but strong associations with other glycemic traits (e.g. HOMA B). All four consortia selected non-redundant SNPs for each locus, if not otherwise stated above.

Consortium	Count	SNP	*P*-value*
DFS	1	rs10830963*	2.5×10^{-7}
DFS	2	rs12682508	3.3×10^{-4}
DFS	3	rs13427272	6.1×10^{-7}
DFS	4	rs1799884***	4.2×10^{-6}
DFS	5	rs42698	6.0×10^{-6}
DFS	6	rs4607517***	2.2×10^{-6}
DFS	7	rs560887**	7.0×10^{-12}
DFS	8	rs6671923	3.5×10^{-6}
DFS	9	rs853787**	1.5×10^{-10}
DFS	10	rs9981885	1.0×10^{-8}
ENGAGE	1	rs10244051	1.5×10^{-5}
ENGAGE	2	rs10282028	1.4×10^{-5}
ENGAGE	3	rs10476552	4.7×10^{-5}
ENGAGE	4	rs1085998	1.9×10^{-5}
ENGAGE	5	rs11614489	2.5×10^{-5}
ENGAGE	6	rs11878620	1.3×10^{-5}
ENGAGE	7	rs1372902	2.3×10^{-5}
ENGAGE	8	rs1387153*	2.2×10^{-17}
ENGAGE	9	rs2129969	7.2×10^{-6}
ENGAGE	10	rs2153977	4.7×10^{-6}
ENGAGE	11	rs2785137	2.5×10^{-5}
ENGAGE	12	rs4147592	3.2×10^{-6}
ENGAGE	13	rs4607517***	5.4×10^{-6}
ENGAGE	14	rs560887**	8.7×10^{-23}
ENGAGE	15	rs6020502	1.1×10^{-5}

ENGAGE	16	rs6702277	7.7×10^{-5}
ENGAGE	17	rs7664714	1.4×10^{-5}
ENGAGE	18	rs7903146	3.1×10^{-7}
ENGAGE	19	rs853778**	4.7×10^{-13}
ENGAGE	20	rs9918832	5.5×10^{-5}
FHS	1	rs234148	5.3×10^{-7}
FHS	2	rs6555474	1.0×10^{-6}
FHS	3	rs563694**	1.4×10^{-6}
FHS	4	rs1450353	2.0×10^{-6}
FHS	5	rs2977451	2.4×10^{-6}
FHS	6	rs12364347	2.5×10^{-6}
FHS	7	rs573225**	6.5×10^{-6}
FHS	8	rs10941189	6.8×10^{-6}
FHS	9	rs1921617	7.1×10^{-6}
FHS	10	rs4969065	7.5×10^{-6}
FHS	11	rs11020107	5.8×10^{-4}
GEM	1	rs10246797	8.7×10^{-8}
GEM	2	rs10497997	1.2×10^{-6}
GEM	3	rs10830963*	7.4×10^{-11}
GEM	4	rs1120557	2.1×10^{-7}
GEM	5	rs11571943	9.4×10^{-7}
GEM	6	rs12285364	4.6×10^{-7}
GEM	7	rs12287852	1.3×10^{-6}
GEM	8	rs12385797	6.7×10^{-7}
GEM	9	rs16993414	5.3×10^{-7}
GEM	10	rs17066694	3.2×10^{-7}
GEM	11	rs339416	8.2×10^{-7}
GEM	12	rs3729709	7.3×10^{-7}
GEM	13	rs4682484	1.7×10^{-7}
GEM	14	rs560887**	6.8×10^{-10}
GEM	15	rs7808025***	1.6×10^{-6}

* SNP representing *MTNR1B* signal.
** SNP representing *G6PC2* signal.
*** SNP representing *GCK* signal.

Supplementary Table 3: Association of (A) rs560887 (*G6PC2*) and (B) rs4607517 (*GCK*) with fasting glucose (G) levels in ten studies within MAGIC.

FG levels (mmol/L) are reported untransformed and unadjusted for covariates. Effect of the risk allele and SE were calculated using untransformed FG values. *P*-values are reported for the additive genetic model with study-specific transformation of FG values, adjusted for gender and age.

(A) **rs560887 (*G6PC2*)**

Study sample	N	**C** allele Frequency	Mean level of FG*** per genotype (SD), mmol/L			Per_allele effect (SE), mmol/L	*P*-value
			TT	**CT**	**CC**		
CoLaus	5,000	0.72	5.27 (0.60)	5.39 (0.70)	5.47 (0.83)	0.091 (0.016)	1.1×10^{-8}
deCODE	6,240	0.70	5.18 (0.71)	5.30 (0.72)	5.40 (0.70)	0.106 (0.014)	7.2×10^{-15}
DGI	1,455	0.70	5.24 (0.55)	5.32 (0.55)	5.32 (0.53)	0.024 (0.021)	0.26
Framingham*	6,479	0.70	5.12 (0.47)	5.17 (0.48)	5.23 (0.48)	0.057 (0.011)	3.0×10^{-16}
FUSION	1,233	0.69	5.24 (0.50)	5.31 (0.48)	5.33 (0.47)	0.036 (0.011)	1.7×10^{-3}
NFBC1966	4,245	0.69	5.58 (0.52)	5.64 (0.46)	5.71 (0.48)	0.065 (0.011)	3.9×10^{-9}
NTR/NESDA	3,166	0.68	5.20 (0.67)	5.22 (0.62)	5.28 (0.64)	0.047 (0.014)	1.1×10^{-3}
Rotterdam	2,058	0.69	5.50 (0.76)	5.66 (0.91)	5.70 (0.84)	0.077 (0.030)	9.0×10^{-3}
Sardinia	4,108	0.63	5.44 (0.88)	5.63 (0.88)	5.75 (0.88)	0.149 (0.023)	1.4×10^{-10}
TwinsUK**	1,828	0.71	4.56 (0.46)	4.62 (0.52)	4.66 (0.59)	0.046 (0.019)	0.014
				Meta-analysis		**0.064 (0.004)**	1.1×10^{-57}

* In Framingham study mean FG values to the imputed SNPs are reported for rs573225 (proxy for rs560887, r^2=0.961).
** In the TwinsUK study, mean FG values per genotype are estimated for a subset of unrelated individuals only.
*** FG levels in NFBC1966 and SardiNIA were measured in whole blood; in other studies, measures were conducted on plasma samples. Values in the table are corrected to plasma FG using a correction factor of 1.13.

(B) **rs4607517 (*GCK*)**

Study sample	N	**A** allele Frequency	Mean level of FG*** per genotype (SD), mmol/L			Per_allele effect (SE), mmol/L	*P*-value
			GG	**AG**	**AA**		
CoLaus	5,000	0.19	5.39 (0.76)	5.48 (0.79)	5.56 (0.71)	0.088 (0.020)	1.0×10^{-5}
deCODE	6,240	0.14	5.32 (0.72)	5.38 (0.71)	5.44 (0.73)	0.060 (0.019)	1.6×10^{-3}
DGI	1,455	0.12	5.29 (0.55)	5.37 (0.52)	5.39 (0.60)	0.073 (0.034)	0.030
Framingham*	6,479	0.18	5.17 (0.49)	5.23 (0.47)	5.31 (0.51)	0.064 (0.024)	1.2×10^{-8}
FUSION	1,233	0.095	5.30 (0.48)	5.36 (0.46)	5.42 (0.42)	0.060 (0.024)	0.011
NFBC1966	4,245	0.12	5.66 (0.49)	5.70 (0.46)	5.81 (0.54)	0.043 (0.015)	4.4×10^{-3}
NTR/NESDA	3,166	0.18	5.22 (0.63)	5.27 (0.63)	5.45 (0.74)	0.073 (0.017)	1.2×10^{-5}
Rotterdam	2,058	0.18	5.66 (0.89)	5.66 (0.77)	5.88 (1.26)	0.040 (0.029)	0.174
Sardinia	4,108	0.17	5.64 (0.89)	5.63 (0.89)	6.01 (0.89)	0.056 (0.016)	6.4×10^{-4}
TwinsUK**	1,828	0.18	4.51 (0.45)	4.63 (0.52)	4.63 (0.58)	0.098 (0.051)	0.054
				Meta-analysis		**0.062 (0.007)**	1.0×10^{-25}

* In Framingham, study mean FG values to the imputed SNPs are reported for rs1799884 (proxy for rs4607517 (r^2=1) **.**

** In the TwinsUK study, mean FG values per genotype are estimated for a subset of unrelated individuals only.

*** FG levels in NFBC1966 and SardiNIA were measured in whole blood; in other studies measures were conducted on plasma samples. Values in the table are corrected to plasma FG using a correction factor of 1.13.

Supplementary Table 4: Secondary analysis: association of lead SNPs with fasting glucose (FG) levels in ten studies after (A) adjustment for body mass index (BMI) and (B) additional exclusion of subjects with FG levels≥7 mmol/L.

(A) Association of rs10830963, rs560887 and rs4607517 with fasting glucose (FG) levels adjusted in addition for body mass index (BMI).

Direction of effect and P-values for the additive genetic model are reported for each study. Only direction of effect is shown (rather than effect size) since incompatible study specific transformations and covariates (as listed in supplementary table 1) were used in the different studies.

"+" indicates that the glucose-raising allele (as designated) is associated with increased levels of the trait.

Study Sample	**N**		rs10830963 **effect allele G#** ***MTNR1B***	rs560887 **effect allele C#** ***G6PC2***	Rs4607517 **effect allele A#** ***GCK***
CoLaus	5,000	Direction of Effect (*P*-value)	+ 2.8×10^{-10}	+ 1.0×10^{-9}	+ 1.6×10^{-5}
deCODE	6,060	Direction of Effect (*P*-value)	+ 1.2×10^{-7}	+ 3.8×10^{-13}	+ 1.4×10^{-3}
DGI	1,455	Direction of Effect (*P*-value)	+ 0.054	+ 0.26	+ 0.030
Framingham	6,470	Direction of Effect (*P*-value)	+ 4.4×10^{-14}	+ 2.9×10^{-19}	+ 5.2×10^{-10}
FUSION	1,233	Direction of Effect (*P*-value)	+ 2.0×10^{-4}	+ 2.6×10^{-3}	+ 0.023
NFBC1966	4,245	Direction of Effect (*P*-value)	+ 4.8×10^{-11}	+ 2.4×10^{-10}	+ 7.4×10^{-3}
NTR/NESDA	3,166	Direction of Effect (*P*-value)	+ 2.5×10^{-3}	+ 1.1×10^{-3}	+ 5.5×10^{-6}
Rotterdam	2,035	Direction of Effect (*P*-value)	+ 1.4×10^{-5}	+ 4.3×10^{-3}	+ 0.091
SardiNIA	4,108	Direction of Effect (*P*-value)	+ 3.2×10^{-4}	+ 1.4×10^{-10}	+ 6.4×10^{-4}
TwinsUK	1,675	Direction of Effect (*P*-value)	+ 6.2×10^{-3}	+ 2.9×10^{-3}	+ 0.93
Meta-analysis	**35,447**	***P*-value**	**2.2×10^{-50}**	**7.6×10^{-62}**	**1.2×10^{-26}**

Allele associated with the higher level of FG.

(B) Association of rs10830963, rs560887, rs4607517 and rs780094 with FG after additional exclusion of subjects with FG levels≥7 mmol/L.

Study Sample	**N**	rs10830963 **effect allele G#** ***MTNR1B***	rs560887 **effect allele C#** ***G6PC2***	rs4607517 **Effect allele A#** ***GCK***	rs780094 **Effect allele C#** ***GCKR***
CoLaus	4,881	7.6×10^{-12}	2.6×10^{-10}	2.0×10^{-7}	0.11
deCODE	6,059	2.8×10^{-7}	5.7×10^{-17}	2.4×10^{-4}	0.019
DGI	1,450	0.060	0.25	0.011	0.092
Framingham	6,479	2.2×10^{-13}	3.0×10^{-16}	1.2×10^{-8}	3.3×10^{-4}
FUSION	1,233	5.8×10^{-4}	1.5×10^{-3}	0.011	0.18
NFBC1966	4,245	1.7×10^{-11}	3.9×10^{-9}	4.4×10^{-3}	0.31
NTR/NESDA	3,122	8.6×10^{-5}	1.6×10^{-4}	4.1×10^{-4}	0.033
Rotterdam	1,853	6.8×10^{-6}	2.5×10^{-5}	0.022	0.43
SardiNIA	4,106	8.7×10^{-4}	1.5×10^{-10}	2.4×10^{-4}	0.018
TwinsUK	1,801	8.9×10^{-3}	2.0×10^{-3}	0.11	0.74
Meta-analysis *P*-value	**35,229**	**1.3×10^{-51}**	**3.1×10^{-66}**	**2.1×10^{-28}**	**8.5×10^{-9}**

Allele associated with the higher level of FG.

Results in this table reflect data sets similar to those in Table 1, with additional exclusion of individuals without known diabetes, but with FG>7mmol/l. In some studies, such exclusion had already been performed in local analyses prior to the meta-analysis, so sample sizes and analyses results match those in Table 1. For other studies, ongoing efforts to harmonize additional aspects of sample ascertainment and data analysis (eg use of covariates), as well as exclusion of individuals with FG>7mmol, explain minor changes in sample size and results compared to table 1.

Supplementary Table 5: Association of rs10830963, rs560887 and rs4607517 with (A) HOMA-B index, (B) fasting insulin and (C) HOMA-IR index in ten studies within MAGIC.

Direction of effect and P-values for the additive genetic model are reported for each study. Only direction of effect is shown (rather than effect size) since incompatible study specific transformations and covariates (as listed in supplementary table 1) were used in the different studies.

(A) HOMA-B

Study Sample	**N**		rs10830963	rs560887	rs4607517
			effect allele G[#]	**effect allele C[#]**	**effect allele A[#]**
			MTNR1B	***G6PC2***	***GCK***
CoLaus	4,421	Direction of Effect	-	-	-
		(*P*-value)	3.3×10^{-4}	1.0×10^{-4}	0.15
deCODE	1,298	Direction of Effect	-	-	+
		(*P*-value)	0.012	3.4×10^{-4}	0.95
DGI	1,368	Direction of Effect	-	-	-
		(*P*-value)	0.52	0.018	0.92
Framingham	2,673	Direction of Effect	-	-	-
		(*P*-value)	3.6×10^{-3}	2.0×10^{-7}	1.2×10^{-3}
FUSION	1,232	Direction of Effect	-	-	-
		(*P*-value)	0.016	7.7×10^{-3}	0.78
NFBC1966	4,223	Direction of Effect	-	-	-
		(*P*-value)	6.2×10^{-5}	1.3×10^{-5}	0.040
NTR/NESDA	1,243	Direction of Effect	-	-	-
		(*P*-value)	0.23	0.044	0.34
Rotterdam	1,774	Direction of Effect	-	-	-
		(*P*-value)	0.050	0.012	0.22
SardiNIA	4,108	Direction of Effect	-	-	-
		(*P*-value)	4.8×10^{-4}	2.6×10^{-5}	0.021
TwinsUK	1,790	Direction of Effect	-	-	-
		(*P*-value)	0.25	0.028	0.28
Meta-analysis	**24,130**	***P*-value**	**1.1×10^{-15}**	**1.2×10^{-26}**	**9.8×10^{-6}**

Allele associated with the higher level of FG.

"-" indicates that the glucose-raising allele (as designated) is associated with decreased levels of the trait (i.e. reduced beta-cell function).

(B) Fasting insulin.

Study Sample	**N**		rs10830963	rs560887	rs4607517
			effect allele G#	**effect allele C#**	**effect allele A#**
			MTNR1B	***G6PC2***	***GCK***
CoLaus	4,575	Direction of effect (*P*-value)	+ 0.91	- 0.73	+ 0.33
deCODE	1,565	Direction of effect (*P*-value)	- 0.71	- 0.58	+ 0.33
DGI	1,388	Direction of effect (*P*-value)	- 0.86	- 0.037	+ 0.47
Framingham	2,675	Direction of effect (*P*-value)	+ 0.15	- 0.097	- 0.81
FUSION	1,234	Direction of effect (*P*-value)	- 0.35	- 0.38	+ 0.43
NFBC1966	4,223	Direction of effect (*P*-value)	+ 0.39	- 0.87	- 0.997
NTR/NESDA	1,277	Direction of Effect (*P*-value)	+ 0.61	- 0.93	+ 0.18
Rotterdam	1,741	Direction of Effect (*P*-value)	- 0.58	+ 0.63	- 0.85
SardiNIA	4,108	Direction of effect (*P*-value)	- 0.26	+ 0.70	- 0.93
TwinsUK	1,828	Direction of effect (*P*-value)	+ 0.80	- 0.85	+ 0.52
Meta-analysis	**24,614**	***P*-value**	**0.90**	**0.17**	**0.19**

Allele associated with the higher level of FG.
"+" indicates that the glucose-raising allele (as designated) is associated with increased levels of the trait.

(C) HOMA-IR

Study Sample	**N**		rs10830963 **effect allele G#** ***MTNR1B***	rs560887 **effect allele C#** ***G6PC2***	rs4607517 **effect allele A#** ***GCK***
CoLaus	4,429	Direction of effect (*P*-value)	+ 0.16	+ 0.33	+ 0.064
deCODE	1,292	Direction of effect (*P*-value)	- 0.69	- 0.49	+ 0.38
DGI	1,393	Direction of effect (*P*-value)	- 0.98	- 0.032	+ 0.40
Framingham	2,675	Direction of effect (*P*-value)	+ 4.9×10^{-3}	- 0.95	+ 0.46
FUSION	1,232	Direction of effect (*P*-value)	- 0.74	- 0.71	+ 0.25
NFBC1966	4,223	Direction of effect (*P*-value)	+ 0.21	+ 0.82	+ 0.85
NTR/NESDA	1,243	Direction of Effect (*P*-value)	+ 0.56	+ 0.99	+ 0.14
Rotterdam	1,765	Direction of Effect (*P*-value)	+ 0.30	+ 0.80	- 0.62
SardiNIA	4,108	Direction of effect (*P*-value)	- 0.88	+ 0.065	+ 0.49
TwinsUK	1,828	Direction of effect (*P*-value)	+ 0.51	+ 0.83	+ 0.36
Meta-analysis	**24,188**	**p-value**	**0.016**	**0.53**	**0.012**

Allele associated with the higher level of FG.

"+" indicates that the glucose-raising allele (as designated) is associated with increased levels of the trait.

Supplementary Table 6: Association of rs10830963, rs560887 and rs4607517 with type 2 diabetes (T2D) in thirteen case-control studies.

Study Sample	N cases/ N controls		rs10830963	rs560887	rs4607517
			FG effect allele G[#]	**FG effect allele C[#]**	**FG effect allele A[#]**
			MTNR1B	***G6PC2***	***GCK***
deCODE	1,465/33,641	OR [95% CI] *P*-value	1.14 (1.03-1.27) 0.013	0.97 (0.88-1.07) 0.52	1.00 (0.88-1.12) 0.95
DGI*	1,464/1,467	OR [95% CI] *P*-value	1.12 (0.96-1.30) 0.095	0.99 (0.86-1.14) 0.97	1.14 (0.94-1.38) 0.11
FUSION	1,161/1,174	OR [95% CI] *P*-value	1.20 (1.03-1.39) 0.018	0.91 (0.80-1.04) 0.15	1.20 (0.99-1.45) 0.064
KORA	433/1,438	OR [95% CI] *P*-value	1.00 (0.84-1.19) 0.96	0.96 (0.81-1.13) 0.63	1.04 (0.85-1.26) 0.71
Rotterdam	1,178/4,761	OR [95% CI] *P*-value	1.17 (1.04-1.30) 0.0066	0.95 (0.86-1.05) 0.29	0.98 (0.87-1.11) 0.80
WTCCC T2D	1,924/2,938	OR [95% CI] *P*-value	1.07 (0.95-1.20) 0.13	0.91 (0.83-1.01) 0.056	0.97 (0.87-1.08) 0.52
CCC	512/499	OR [95% CI] *P*-value	1.07 (0.88-1.30) 0.49	0.84 (0.69-1.01) 0.069	1.33 (1.05-1.67) 0.015
ADDITION/ELY	852/1,593	OR [95% CI] *P*-value	1.16 (1.02-1.33) 0.027	0.89 (0.79-1.01) 0.079	1.22 (1.04-1.43) 0.011
Norfolk	2,796/2,288	OR [95% CI] *P*-value	1.00 (0.90-1.10) 0.97	-	1.02 (0.92-1.15) 0.67
UKT2DGC	4,124/5,111	OR [95% CI] *P*-value	1.03 (0.96-1.10) 0.38	-	-
OxGN/58BC	335/5,334	OR [95% CI] *P*-value	0.91 (0.75-1.10) 0.32	-	-
FUSION Stage 2	1,199/1,258	OR [95% CI] *P*-value	1.15 (1.02-1.30) 0.022	-	-
METSIM	793/2,951	OR [95% CI] *P*-value	1.16 (1.03-1.30) 0.014	-	-
Meta-analysis**	**18,236/64,453**	**OR [95% CI] *P*-value**	**1.09 (1.05-1.12) 3.3 x 10^{-7}**	**0.93 (0.89-0.97) 0.0017**	**1.05 (1.00-1.10) 0.031**

Allele associated with higher FG level in the MAGIC meta-analysis. Odds Ratios reflect effect of this allele on T2D risk compared to the other allele as reference.

*ORs are reported for DGI unrelated case-control sample only (n=2097), *P*-values are reported for entire sample.
**Combined estimates of Odds Ratios (OR) were calculated using a fixed-effects, inverse-variance meta-analysis; *P*-values were derived from a z-score weighted meta-analysis across all samples.