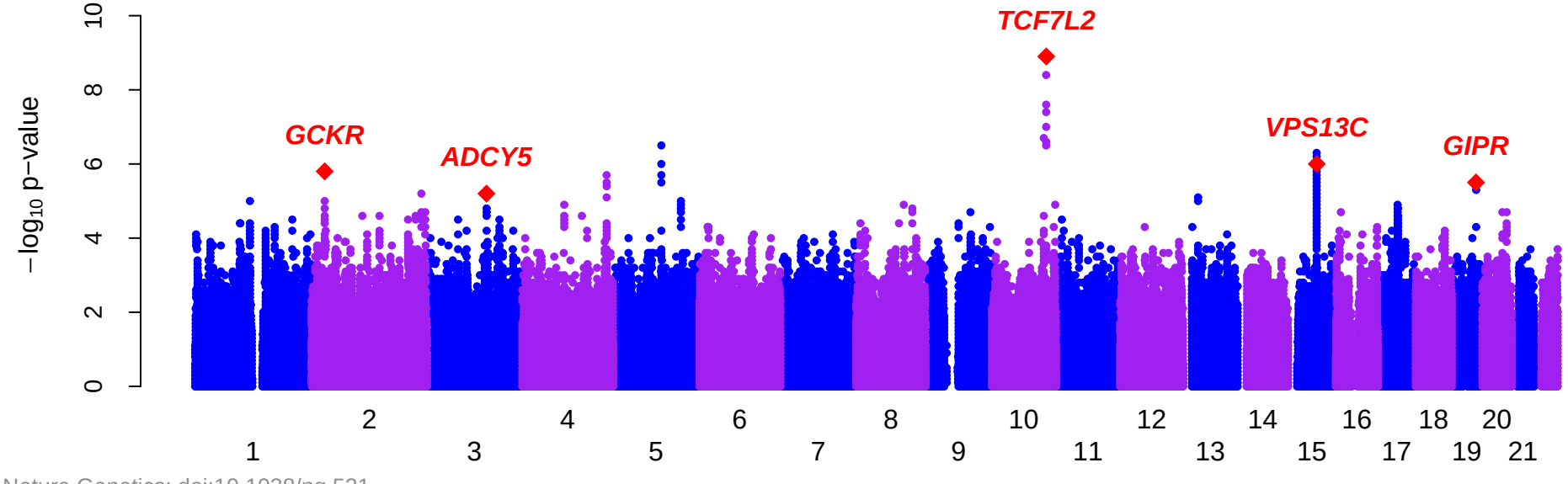
Supplementary Information for Genetic Variation in Gastric Inhibitory Polypeptide Receptor (*GIPR*) Impacts the Glucose and Insulin Responses to an Oral Glucose Challenge

Richa Saxena*, Marie-France Hivert*, Claudia Langenberg, Toshiko Tanaka, James S Pankow, Peter Vollenweider, Valeriya Lyssenko, Nabila Bouatia-Naji, Josée Dupuis, Anne U Jackson, W H Linda Kao-, Man Li, Nicole L Glazer, Alisa K Manning , Jian'an Luan, Heather M Stringham, Inga Prokopenko, Toby Johnson, Niels Grarup, Trine Boesgaard, Cécile Lecoeur, Peter Shrader, Jeffrey O'Connell, Erik Ingelsson, David J Couper, Kenneth Rice, Kijoung Song, Camilla H Andreasen, Christian Dina, Anna Köttgen, Olivier Le Bacquer, François Pattou, Jalal Taneera, Valgerdur Steinthorsdottir, Denis Rybin, Kristin Ardlie, Michael Sampson, Lu Qi, Mandy van Hoek, Michael N Weedon, Yurii S Aulchenko, Benjamin F Voight, Harald Grallert, Beverley Balkau, Richard N Bergman, Suzette J Bielinski, Amelie Bonnefond, Lori L Bonnycastle, Knut Borch-Johnsen, Yvonne Böttcher, Eric Brunner, Thomas A Buchanan, Suzannah J Bumpstead, Christine Cavalcanti-Proença, Guillaume Charpentier, Yii-Der Ida Chen, Peter S Chines, Francis S Collins, Marilyn Cornelis, Gabriel J Crawford, Jerome Delplanque, Alex Doney, Josephine M Egan, Michael R Erdos, Mathieu Firmann, Nita G Forouhi, Caroline S Fox, Mark O Goodarzi, Jürgen Graessler, Aroon Hingorani, Bo Isomaa, Torben Jørgensen, Mika Kivimaki, Peter Kovacs, Knut Krohn, Meena Kumari, Torsten Lauritzen, Claire Lévy-Marchal, Vladimir Mayor, Jarred B McAteer, David Meyre, Braxton D Mitchell, Karen L Mohlke, Mario A Morken, Narisu Narisu, Colin N A Palmer, Ruth Pakyz, Laura Pascoe, Felicity Payne, Daniel Pearson, Wolfgang Rathmann, Annelli Sandbaek, Avan Aihie Sayer, Laura J Scott, Stephen J Sharp, Eric Sijbrands, Andrew Singleton, David S Siscovick, Nicholas L Smith, Thomas Sparsø, Amy J Swift, Holly Syddall, Gudmar Thorleifsson, Anke Tönjes, Tiinamaija Tuomi, Jaakko Tuomilehto, Timo T Valle, Gérard Waeber, Andrew Walley, Dawn M Waterworth, Eleftheria Zeggini, Jing Hua Zhao, GIANT consortium, Thomas Illig, H Erich Wichmann, James F Wilson, Cornelia van Duijn, Frank B Hu, Andrew D Morris, Timothy M Frayling, Andrew T Hattersley, Unnur Thorsteinsdottir, Kari Stefansson, Peter Nilsson, Ann-Christine Syvänen, Alan R Shuldiner, Mark Walker, Stefan R Bornstein, Peter Schwarz, Gordon H Williams, David M Nathan, Johanna Kuusisto, Markku Laakso, Cyrus Cooper, Michael Marmot, Luigi Ferrucci, Vincent Mooser, Michael Stumvoll, Ruth JF Loos, David Altshuler, Bruce M Psaty, Jerome I Rotter, Eric Boerwinkle, Torben Hansen, Oluf Pedersen, Jose C Florez, Mark I McCarthy, Michael Boehnke, Inês Barroso, Robert Sladek, Philippe Froguel, James B Meigs, Leif Groop, Nicholas J Wareham and Richard M Watanabe, for the MAGIC investigators.

*these authors contributed equally

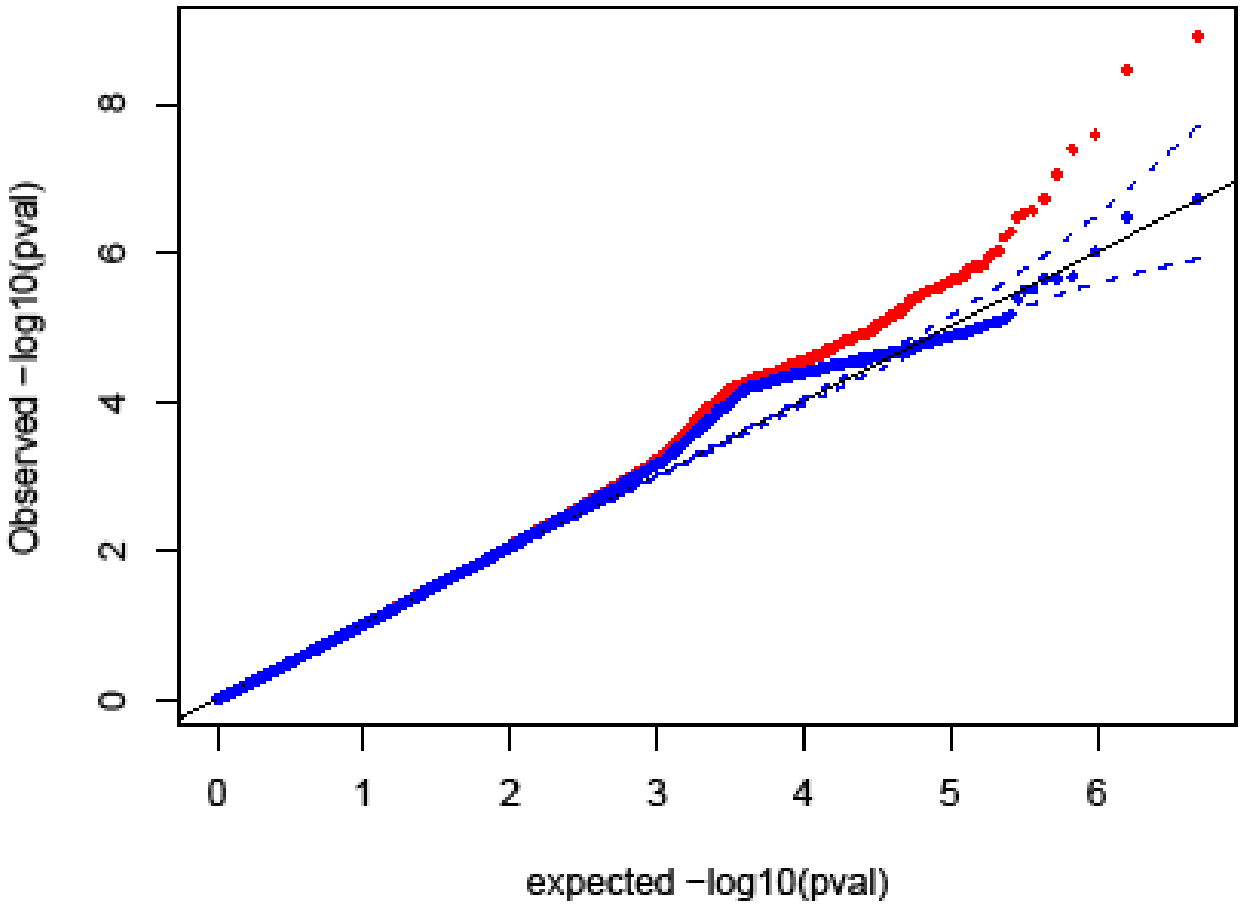
Nature Genetics: doi:10.1038/ng.521

Supplementary Figure 1. Manhattan and QQ plots of the association *P* values for 2-hr glucose (BMI-adjusted) in the discovery meta-analysis of 9 GWAS, (a) Manhattan plot. Directly genotyped and imputed SNPs are plotted with their meta-analysis *P* values (as –log10 values) as a function of genomic position (NCBI Build 36; hg18). SNPs that achieved genome-wide significance in combined discovery and replication meta-analyses are highlighted. The strong signal on chr 5 represents the *SLCO4C1* locus, which was highly significant in the discovery sample, but did not replicate and did not remain genome-wide significant. Note that SNPs were selected for replication based on four interim z-score based analyses. (b) Quantile-quantile (Q-Q) plot. The expected null distribution is plotted along the black diagonal, the entire distribution of observed *P* values is plotted in red (λ=1.008), and a distribution that excludes the five novel 2-hr glucose loci is plotted in blue (λ=1.007). Blue dashed lines represent 95% confidence intervals for the null distribution. The observed deviation from expectation in both distributions could represent additional loci that await discovery in studies with greater statistical power.



Nature Genetics: doi:10.1038/ng.521

b



Nature Genetics: doi:10.1038/ng.521

Supplementary Table 2. Meta-analysis of association results for 2-hr glucose across discovery and replication cohorts.

SNP	Chr	Position (NCBI B36) (bp)	Nearest Gene	Effect Allele/ non-effect allele	Effect allele frequency	Discovery (BMI-adj)				Replication (BMI-adj)				Discovery + Replication (BMI-adj)					Discovery + Replication				
						N	Effect	(SE)	*p* -value	N	Effect	(SE)	*p* -value	N	Effect	(SE)	*p* -value	*p* -value$_{het}$	N	Effect	(SE)	*p* -value	*p* -value$_{het}$
rs17187140	1	206,376,398	*PLXNA2*	a/g	0.1	13,563	0.15	0.037	$6.29x10^{-5}$	13,377	-0.04	0.029	0.12	26,940	0.03	0.023	0.21	0.015	26,453	0.03	0.023	0.18	0.011
rs1260326	**2**	**27,584,444**	***GCKR***	**t/c**	0.40	**15,234**	**0.09**	**0.019**	$\mathbf{1.53x10^{-6}}$	**23,166**	**0.06**	**0.014**	$\mathbf{5.33x10^{-6}}$	**38,400**	**0.07**	**0.011**	$\mathbf{7.05x10^{-11}}$	**0.092**	**37,928**	**0.07**	**0.011**	$\mathbf{3.0x10^{-10}}$	**0.1092**
rs4971652	2	50,245,662	*NRXN1*	a/g	0.84	15,184	0.10	0.026	$2.20x10^{-4}$	12,173	0.01	0.027	0.82	27,357	0.05	0.019	$5.53x10^{-3}$	0.19	26,873	0.05	0.019	$4.21x10^{-3}$	0.093
rs12618178	2	54,908,792	*?*	a/c	0.20	15,234	-0.09	0.024	$1.04x10^{-4}$	14,354	0.01	0.022	0.63	29,588	-0.04	0.016	0.023	0.011	29,129	-0.04	0.016	0.014	$8.94x10^{-3}$
rs7604361	2	106,068,242	*(C2orf40)*	t/g	0.01	12,131	0.49	0.116	$2.71x10^{-5}$	9,707	0.03	0.107	0.77	21,838	0.24	0.079	$2.23x10^{-3}$	0.012	21,880	0.23	0.079	$4.14x10^{-3}$	0.011
rs16847412	2	142,335,384	*LRP1B*	t/c	0.93	15,234	-0.14	0.032	$2.33x10^{-5}$	17,104	-0.03	0.024	0.22	32,338	-0.07	0.019	$4.56x10^{-4}$	0.05	32,382	-0.07	0.020	$6.12x10^{-4}$	0.027
rs1955086	2	222,400,290	*(EPHA4)*	t/c	0.75	15,234	-0.08	0.023	$2.22x10^{-4}$	21,758	0.00	0.014	0.73	36,992	-0.03	0.012	0.025	0.11	36,542	-0.03	0.012	0.028	0.18
rs6726280	2	230,201,928	*DNER*	a/c	0.17	15,234	0.12	0.027	$6.71x10^{-6}$	23,448	0.01	0.016	0.71	38,682	0.04	0.014	$8.35x10^{-3}$	$1.39x10^{-3}$	38,202	0.04	0.014	$9.40x10^{-3}$	$3.24x10^{-4}$
rs12374129	3	78,626,542	*(ROBO1)*	t/c	0.15	15,234	0.09	0.023	$2.55x10^{-4}$	12,239	-0.02	0.023	0.42	27,473	0.03	0.016	0.049	0.17	27,297	0.04	0.016	0.018	0.26
rs2877716	**3**	**124,577,141**	***ADCY5***	**t/c**	**0.23**	**15,214**	**-0.10**	**0.022**	$\mathbf{6.26x10^{-6}}$	**29,483**	**-0.09**	**0.013**	$\mathbf{1.21x10^{-11}}$	**44,697**	**-0.09**	**0.011**	$\mathbf{4.19x10^{-16}}$	$\mathbf{5.85x10^{-8}}$	**44,225**	**-0.09**	**0.011**	$\mathbf{7.41x10^{-16}}$	$\mathbf{3.17x10^{-7}}$
rs9845279	3	158,795,136	*(C3orf55)*	c/g	0.56	12,909	-0.10	0.026	$9.46x10^{-5}$	12,017	0.00	0.018	0.99	24,926	-0.03	0.015	0.023	$1.57x10^{-4}$	24,438	-0.03	0.015	0.022	$2.97x10^{-4}$
rs309795	4	177,703,271	*(VEGFC)*	a/c	0.43	15,234	-0.09	0.019	$2.22x10^{-6}$	14,529	0.01	0.017	0.44	29,763	-0.03	0.013	$9.44x10^{-3}$	$1.30x10^{-4}$	29,284	-0.03	0.013	0.02	$1.25x10^{-4}$
rs10037968	5	101,582,380	*(SLCO4C1)*	t/c	0.99	15,234	0.19	0.037	$3.31x10^{-7}$	21,689	0.03	0.021	0.10	36,923	0.07	0.019	$7.49x10^{-5}$	$1.79x10^{-3}$	36,423	0.07	0.019	$2.86x10^{-4}$	$4.05x10^{-3}$
rs13265179	8	9,232,104	*PPP1R3B*	a/c	0.10	15,234	-0.11	0.028	$1.18x10^{-4}$	6,958	-0.09	0.049	0.064	22,192	-0.10	0.024	$2.06x10^{-5}$	0.21	22,023	-0.11	0.025	$1.69x10^{-5}$	0.12
rs12545656	8	99,548,888	*STK3*	a/g	0.93	15,234	-0.19	0.043	$1.28x10^{-5}$	14,533	-0.01	0.037	0.85	29,767	-0.08	0.028	$2.71x10^{-3}$	$9.77x10^{-3}$	29,288	-0.08	0.029	$4.63x10^{-3}$	$4.06x10^{-3}$
rs2439649	9	110,915,284	*C9orf5*	a/g	0.58	15,234	-0.07	0.019	$2.22x10^{-4}$	14,053	0.00	0.018	0.86	29,287	-0.03	0.013	$7.87x10^{-3}$	0.023	28,796	-0.04	0.013	$6.26x10^{-3}$	0.013
rs12243326	**10**	**114,778,805**	***TCF7L2***	**t/c**	**0.79**	**15,215**	**-0.13**	**0.022**	$\mathbf{1.20x10^{-9}}$	**23,351**	**-0.05**	**0.017**	$\mathbf{1.27x10^{-3}}$	**38,566**	**-0.08**	**0.013**	$\mathbf{4.23x10^{-10}}$	$\mathbf{1.08x10^{-3}}$	**38,078**	**-0.07**	**0.013**	$\mathbf{1.12x10^{-7}}$	$\mathbf{1.76x10^{-3}}$
rs12873155	13	31,609,703	*FRY*	t/c	0.40	15,234	0.09	0.019	$8.81x10^{-6}$	11,584	0.00	0.023	0.88	26,818	0.05	0.015	$1.05x10^{-3}$	0.075	26,358	0.04	0.015	$3.31x10^{-3}$	0.041
rs2585509	13	77,590,882	*(EDNRB)*	t/c	0.31	15,234	-0.08	0.020	$1.65x10^{-4}$	9,791	-0.02	0.029	0.53	25,025	-0.06	0.017	$5.86x10^{-4}$	0.23	24,526	-0.06	0.017	$2.05x10^{-4}$	0.3
rs17271305	**15**	**60,120,272**	***VPS13C***	**a/g**	**0.58**	**15,234**	**-0.09**	**0.019**	$\mathbf{1.04x10^{-6}}$	**15,633**	**-0.05**	**0.015**	$\mathbf{1.58x10^{-3}}$	**30,867**	**-0.06**	**0.012**	$\mathbf{4.11x10^{-8}}$	**0.22**	**30,906**	**-0.06**	**0.012**	$\mathbf{1.30x10^{-7}}$	**0.075**
rs12448015	16	22,665,124	*(HS3ST2)*	a/g	0.97	15,234	-0.21	0.052	$7.42x10^{-5}$	8,575	-0.18	0.090	0.043	23,809	-0.20	0.045	$8.93x10^{-6}$	0.042	23,299	-0.20	0.046	$1.46x10^{-5}$	0.027
rs7184872	16	27,374,838	*(GTF3C1)*	t/g	0.84	15,234	-0.11	0.030	$3.01x10^{-4}$	23,660	0.01	0.016	0.59	38,894	-0.02	0.014	0.21	0.15	38,421	-0.02	0.014	0.11	0.098
rs1060253	16	86,423,639	*SLC7A5*	c/g	0.32	15,234	0.09	0.022	$5.08x10^{-5}$	14,598	-0.02	0.019	0.23	29,832	0.03	0.014	0.073	$8.41x10^{-4}$	29,345	0.01	0.015	0.33	$3.69x10^{-4}$
rs17426106	17	41,184,706	*CRHR1*	c/g	0.22	10,031	-0.11	0.026	$3.21x10^{-5}$	11,733	-0.01	0.029	0.69	21,764	-0.07	0.020	$8.34x10^{-4}$	0.012	21,278	-0.06	0.020	$1.10x10^{-3}$	0.026
rs9952194	18	55,862,008	*(PMAIP1)*	t/c	0.79	15,234	0.08	0.021	$9.33x10^{-5}$	11,443	0.01	0.023	0.78	26,677	0.05	0.016	$2.28x10^{-3}$	0.22	26,167	0.05	0.016	$8.54x10^{-4}$	0.16
rs12985777	19	2,219,055	*?*	t/c	0.26	15,200	0.07	0.022	$2.31x10^{-3}$	9,663	0.05	0.032	0.090	24,863	0.06	0.018	$5.19x10^{-4}$	0.59	24,368	0.06	0.019	$1.10x10^{-3}$	0.57
rs4804519	19	10,669,770	*QTRT1*	t/c	0.63	15,234	0.07	0.020	$3.31x10^{-4}$	12,987	0.01	0.022	0.65	28,221	0.04	0.015	$3.07x10^{-3}$	0.49	28,266	0.04	0.015	$3.34x10^{-3}$	0.59
rs10423928	**19**	**50,874,144**	***GIPR***	**a/t**	**0.18**	**11,268**	**0.15**	**0.032**	$\mathbf{3.33x10^{-6}}$	**30,620**	**0.09**	**0.013**	$\mathbf{2.30x10^{-11}}$	**41,888**	**0.09**	**0.012**	$\mathbf{1.98x10^{-15}}$	$\mathbf{1.85x10^{-5}}$	**41,099**	**0.08**	**0.012**	$\mathbf{3.20x10^{-12}}$	$\mathbf{8.21x10^{-5}}$
rs2822664	21	14,743,816	*SAMSN1*	a/g	0.97	12,130	-0.25	0.073	$6.53x10^{-4}$	10,242	-0.07	0.075	0.37	22,372	-0.16	0.052	$2.12x10^{-3}$	0.29	21,872	-0.14	0.053	$7.18x10^{-3}$	0.24

						models with further adjustment for fasting glucose															
						Discovery (FG-adj, BMI-adj)				Replication (FG-adj, BMI-adj)				Discovery + Replication (FG-adj, BMI-adj)					Discovery + Replication (FG-adj)				
SNP	Chr	Position (NCBI B36) (bp)	Nearest Gene	Effect Allele/ non-	Effect allele frequency	N	Effect (SE)		*p* -value	N	Effect (SE)		*p* -value	N	Effect (SE)		*p* -value	*p* -value$_{het}$	N	Effect (SE)		*p* -value	*p* -value$_{het}$
rs17187140	1	206,376,398	*PLXNA2*	a/g	0.1	13,358	0.15	0.036	3.37×10^{-5}	13,939	-0.04	0.028	0.14	27,297	0.03	0.022	0.16	0.016	26,819	0.03	0.023	0.14	8.21×10^{-3}
rs1260326	**2**	**27,584,444**	***GCKR***	**t/c**	0.40	**15,029**	**0.12**	**0.018**	**3.77×10^{-11}**	**22,624**	**0.09**	**0.014**	**1.04×10^{-11}**	**37,653**	**0.10**	**0.011**	**9.23×10^{-21}**	**0.099**	**37,181**	**0.11**	**0.011**	**2.26×10^{-21}**	**0.10**
rs4971652	2	50,245,662	*NRXN1*	a/g	0.84	14,979	0.08	0.026	1.14×10^{-3}	11,658	0.01	0.026	0.76	26,637	0.05	0.018	0.011	0.26	26,673	0.05	0.018	0.011	0.16
rs12618178	2	54,908,792	*?*	a/c	0.20	15,029	-0.09	0.023	5.03×10^{-5}	13,840	0.01	0.021	0.56	28,869	-0.04	0.016	0.02	0.014	28,390	-0.04	0.016	0.015	8.37×10^{-3}
rs7604361	2	106,068,242	*(C2orf40)*	t/g	0.01	10,696	0.53	0.120	9.43×10^{-6}	10,803	0.06	0.105	0.56	21,499	0.27	0.079	7.74×10^{-4}	3.79×10^{-3}	21,016	0.24	0.080	3.32×10^{-3}	4.29×10^{-3}
rs16847412	2	142,335,384	*LRP1B*	t/c	0.93	15,029	-0.12	0.032	1.64×10^{-4}	17,087	-0.02	0.024	0.33	32,116	-0.06	0.019	2.41×10^{-3}	0.036	31,634	-0.06	0.019	3.78×10^{-3}	0.018
rs1955086	2	222,400,290	*(EPHA4)*	t/c	0.75	15,029	-0.08	0.022	2.38×10^{-4}	21,241	-0.01	0.014	0.62	36,270	-0.03	0.012	0.018	0.070	35,793	-0.02	0.012	0.037	0.11
rs6726280	2	230,201,928	*DNER*	a/c	0.17	15,029	0.11	0.026	3.45×10^{-5}	22,903	0.01	0.016	0.71	37,932	0.03	0.014	0.013	0.014	37,455	0.03	0.014	0.02	6.46×10^{-3}
rs12374129	3	78,626,542	*(ROBO1)*	t/c	0.15	15,029	0.07	0.023	1.98×10^{-3}	11,912	-0.02	0.022	0.38	26,941	0.02	0.016	0.12	0.27	26,889	0.03	0.016	0.072	0.42
rs2877716	**3**	**124,577,141**	***ADCY5***	**t/c**	**0.23**	**15,009**	**-0.08**	**0.022**	**2.24×10^{-4}**	**28,938**	**-0.07**	**0.013**	**1.65×10^{-8}**	**43,947**	**-0.07**	**0.011**	**1.68×10^{-11}**	**4.74×10^{-8}**	**43,480**	**-0.08**	**0.011**	**7.98×10^{-12}**	**2.14×10^{-7}**
rs9845279	3	158,795,136	*(C3orf55)*	c/g	0.56	12,704	-0.10	0.025	4.03×10^{-5}	12,596	-0.01	0.018	0.71	25,300	-0.04	0.015	7.14×10^{-3}	4.61×10^{-4}	25,342	-0.04	0.015	6.76×10^{-3}	9.44×10^{-4}
rs309795	4	177,703,271	*(VEGFC)*	a/c	0.43	15,029	-0.09	0.019	5.59×10^{-6}	12,891	0.01	0.017	0.49	27,920	-0.03	0.013	9.81×10^{-3}	1.06×10^{-4}	28,545	-0.03	0.013	0.017	2.09×10^{-4}
rs10037968	5	101,582,380	*(SLCO4C1)*	t/c	0.99	15,029	0.20	0.036	2.14×10^{-8}	21,129	0.03	0.021	0.094	36,158	0.08	0.018	2.17×10^{-5}	6.18×10^{-4}	35,674	0.07	0.018	4.91×10^{-5}	8.25×10^{-4}
rs13265179	8	9,232,104	*PPP1R3B*	a/c	0.10	15,029	-0.12	0.027	2.50×10^{-5}	6,745	-0.13	0.047	6.60×10^{-3}	21,774	-0.12	0.024	5.24×10^{-7}	0.18	21,815	-0.12	0.024	3.10×10^{-7}	0.13
rs12545656	8	99,548,888	*STK3*	a/g	0.93	15,029	-0.17	0.042	3.25×10^{-5}	13,999	-0.01	0.037	0.86	29,028	-0.08	0.028	4.29×10^{-3}	0.014	28,549	-0.08	0.028	5.07×10^{-3}	3.92×10^{-4}
rs2439649	9	110,915,284	*C9orf5*	a/g	0.58	15,029	-0.07	0.018	4.81×10^{-5}	13,507	0.00	0.017	0.97	28,536	-0.04	0.013	4.51×10^{-3}	5.62×10^{-3}	28,588	-0.04	0.013	4.58×10^{-3}	3.11×10^{-3}
rs12243326	**10**	**114,778,805**	***TCF7L2***	**t/c**	**0.79**	**15,010**	**-0.12**	**0.021**	**3.69×10^{-9}**	**22,790**	**-0.05**	**0.016**	**5.32×10^{-3}**	**37,800**	**-0.07**	**0.013**	**9.99×10^{-9}**	**3.16×10^{-3}**	**37,326**	**-0.08**	**0.013**	**1.17×10^{-10}**	**0.24**
rs12873155	13	31,609,703	*FRY*	t/c	0.40	15,029	0.08	0.019	7.09×10^{-6}	11,070	0.00	0.022	0.83	26,099	0.05	0.014	3.70×10^{-4}	0.12	25,628	0.05	0.015	8.20×10^{-4}	0.067
rs2585509	13	77,590,882	*(EDNRB)*	t/c	0.31	15,029	-0.06	0.020	9.72×10^{-4}	9,245	-0.01	0.028	0.75	24,274	-0.05	0.016	4.03×10^{-3}	0.27	23,788	-0.05	0.016	3.09×10^{-3}	0.24
rs17271305	**15**	**60,120,272**	***VPS13C***	**a/g**	**0.58**	**15,029**	**-0.11**	**0.018**	**8.52×10^{-9}**	**15,615**	**-0.05**	**0.014**	**9.97×10^{-5}**	**30,644**	**-0.07**	**0.011**	**4.33×10^{-11}**	**0.29**	**29,680**	**-0.07**	**0.011**	**8.41×10^{-11}**	**0.11**
rs12448015	16	22,665,124	*(HS3ST2)*	a/g	0.97	15,029	-0.19	0.051	2.35×10^{-4}	8,034	-0.15	0.086	0.082	23,063	-0.18	0.044	5.12×10^{-5}	0.15	22,621	-0.17	0.044	8.44×10^{-5}	0.12
rs7184872	16	27,374,838	*(GTF3C1)*	t/g	0.84	15,029	-0.11	0.029	7.72×10^{-5}	23,119	0.01	0.016	0.59	38,148	-0.02	0.014	0.15	0.084	37,193	-0.03	0.014	0.06	0.11
rs1060253	16	86,423,639	*SLC7A5*	c/g	0.32	15,029	0.09	0.021	1.25×10^{-5}	14,057	-0.05	0.019	8.10×10^{-3}	29,086	0.01	0.014	0.35	1.00×10^{-4}	28,131	0.02	0.014	0.23	8.07×10^{-5}
rs17426106	17	41,184,706	*CRHR1*	c/g	0.22	10,007	-0.11	0.025	2.01×10^{-5}	11,192	0.00	0.028	0.88	21,199	-0.06	0.019	1.16×10^{-3}	3.19×10^{-3}	20,235	-0.05	0.019	6.29×10^{-3}	0.021
rs9952194	18	55,862,008	*(PMAIP1)*	t/c	0.79	15,029	0.07	0.021	3.18×10^{-4}	10,902	0.01	0.022	0.55	25,931	0.05	0.015	2.26×10^{-3}	0.55	25,489	0.05	0.015	9.00×10^{-4}	0.50
rs12985777	19	2,219,055	*?*	t/c	0.26	14,995	0.08	0.022	1.18×10^{-4}	9,121	0.05	0.030	0.11	24,116	0.07	0.018	4.48×10^{-5}	0.37	23,153	0.07	0.018	5.28×10^{-5}	0.41
rs4804519	19	10,669,770	*QTRT1*	t/c	0.63	15,029	0.08	0.019	3.94×10^{-5}	12,979	0.01	0.021	0.58	28,008	0.05	0.014	6.32×10^{-4}	0.22	27,049	0.05	0.015	5.28×10^{-4}	0.21
rs10423928	**19**	**50,874,144**	***GIPR***	**a/t**	**0.18**	**11,066**	**0.16**	**0.030**	**1.04×10^{-7}**	**29,762**	**0.10**	**0.013**	**6.33×10^{-15}**	**40,828**	**0.11**	**0.012**	**2.56×10^{-20}**	**3.08×10^{-5}**	**40,354**	**0.10**	**0.012**	**5.943×10^{-18}**	**4.96×10^{-5}**
rs2822664	21	14,743,816	*SAMSN1*	a/g	0.97	11,928	-0.28	0.070	1.43×10^{-5}	10,815	-0.07	0.073	0.35	22,743	-0.18	0.050	3.20×10^{-4}	0.21	22,301	-0.17	0.051	6.00×10^{-4}	0.14

Chromosomal position is listed according to NCBI build 36 (hg18). The gene closest to the SNP is indicated, a gene name without parenthesis indicates that the lead SNP resides within the listed gene, whereas a gene in parenthesis indicates the closest gene to an intergenic SNP. Effect allele/non-effect allele are defined based on the positive strand of NCBI build 36 (hg18). Effect allele frequencies are from the HapMap phase II CEU sample. Results from the inverse-variance meta-analysis are presented for the discovery samples. A standard set of SNP proxies (with r^2>0.8 in HapMap phase II CEU samples were genotyped when the primary SNP failed in replication studies). *P* -value$_{het}$ is the *P* value for heterogeneity across joint discovery and replication samples based on the Q statistic. *ADCY5* and *GIPR* SNPs displayed evidence of heterogeneity, and may reflect a differential effect of these SNPs on study samples with primarily normal glucose tolerant (NGT) vs. impaired glucose tolerant (IGT) individuals. All analyses are adjusted for sex, age, study-specific covariates. BMI-adj: these analyses are adjusted for sex, age, study-specific covariates and body mass index. FG-adj: these analyses are adjusted for fasting glucose, sex, age, study-specific covariates.

Supplementary Table 3. Association of 2hr-glucose SNPs with glycemic traits in MAGIC and body mass index (BMI) in GIANT discovery meta-analyses

Chr	SNP	Nearest gene	Effect Allele/ Non-effect Allele		fasting glucose (mmol/L)	HOMA-B	fasting insulin (pmol/L)	HOMA-IR	HbA1c (%)	BMI (kg/m^2)
2	rs1260326	*GCKR*	T/C	Effect (SE)	-0.027 (0.004)	-0.003 (0.003)	-0.015 (0.004)	-0.020 (0.004)	-0.004 (0.006)	0.012 (0.009)
				P -value	4.3×10^{-13}	0.33	1.2×10^{-4}	9.2×10^{-7}	0.53	0.17
3	rs2877716	*ADCY5*	C/T	Effect (SE)	0.023 (0.004)	-0.013 (0.004)	-0.001 (0.005)	0.002 (0.005)	0.012 (0.007)	-0.0057(0.010)
				P -value	1.4×10^{-7}	1.5×10^{-3}	0.86	0.66	0.068	0.59
10	rs12243326	*TCF7L2*	C/T	Effect (SE)	0.021 (0.004)	-0.019 (0.004)	-0.011 (0.005)	-0.009 (0.005)	0.017 (0.006)	-0.033 (0.009)
				P -value	6.2×10^{-7}	1.9×10^{-6}	0.016	0.058	5.0×10^{-3}	4.4×10^{-4}
15	rs17271305	*VPS13C*	G/A	Effect (SE)	-0.009 (0.004)	0.004 (0.003)	0.001 (0.004)	-0.001 (0.004)	0.007 (0.006)	0.006 (0.009)
				P -value	0.022	0.23	0.79	0.73	0.20	0.49
19	rs10423928	*GIPR*	A/T	Effect (SE)	-0.013 (0.005)	0.001 (0.004)	-0.004 (0.005)	-0.005 (0.006)	0.021 (0.015)	-0.140 (0.035)**
				P -value	0.014	0.86	0.46	0.32	0.16	7.5×10^{-5}
				N	34,380-46,240	25,902-36,661	27,315-38,390	26,022-37,127	4,168-17,218	28,225-32,530

Effect allele raises 2h glucose; GIANT consortium BMI association data from Willer et al., 2009 (ref.14 in main text); **data for *GIPR* were not available from the GIANT consortium, and are from Lyssenko et al. (submitted) from a Swedish meta-analysis for N=27,628 .

Nature Genetics: doi:10.1038/ng.521

Supplementary Table 4. Association of rs10423928 [*GIPR*], rs17271305 [*VPS13C*] and rs2877716 [*ADCY5*] with insulinogenic index, AUC (area under the curve) insulin/ glucose, and 2h insulin (adjusted for 2h glucose) within MAGIC and meta-analysis across all studies.

	***GIPR* SNP rs10423928 A**				***ADCY5* SNP rs2877716 C**				***VPS13C* SNP rs17271305 G**			
Study sample	N	Per allele effect (SE) (BMI adj.)	*P*-value (BMI adj.)	*P*-value	N	Per allele effect (SE) (BMI adj.)	*P*-value (BMI adj.)	*P*-value	N	Per allele effect (SE) (BMI adj.)	*P*-value (BMI adj.)	*P*-value
Insulinogenic index (μU/mmol) [1]												
AMISH	674	-0.075 (0.073)	0.61	0.42	527**	-0.004 (0.067)	0.98	0.76	675	-0.142 (0.050)	0.16	0.11
BotniaPPP	4,241	-0.074 (0.018)	$4.5x10^{-5}$	$8.7x10^{-6}$	2,811**	-0.029 (0.028)	0.3	0.31	4,121***	0.014 (0.016)	0.4	0.37
DIAGEN	943	-0.077 (0.040)	0.057	0.066	922**	-0.005 (0.042)	0.99	0.98	-	-	-	-
Ely	1,306*	-0.127 (0.035)	$2.43x10^{-4}$	$7.82x10^{-5}$	1,360	-0.042 (0.030)	0.16	0.076	-	-	-	-
French Family Members	233	0.090 (0.112)	0.43	0.45	228	0.100 (0.126)	0.43	0.35	216	-0.080 (0.110)	0.44	0.45
French Haguenau	1,244	-0.003 (0.039)	0.94	0.9	1,243	-0.037 (0.037)	0.32	0.19	1,259	0.015 (0.032)	0.63	0.64
French Obese Adults	206	-0.196 (0.121)	0.107	0.07	-	-	-	-	-	-	-	-
Hertfordshire Study	996*	-0.067 (0.042)	0.11	0.12	977	-0.052 (0.037)	0.16	0.25	-	-	-	-
Inter99	5,016	-0.117 (0.023)	$2.68x10^{-7}$	$3.91x10^{-7}$	5,059	0.020 (0.021)	0.34	0.26	5,013	0.042 (0.019)	0.029	0.06
METSIM	4,998	-0.057 (0.018)	0.0013	$2.98x10^{-4}$	5,034**	-0.009 (0.020)	0.64	0.77	-	-	-	-
RISC	1,168	-0.063 (0.035)	0.072	0.027	1,164	-0.022 (0.033)	0.508	0.42	1,153	-0.002 (0.029)	0.94	0.85
ROCHE	545	-0.033 (0.063)	0.61	0.37	551	-0.011 (0.059)	0.85	0.74	551	-0.005 (0.052)	0.92	0.85
ULSAM	922	-0.104 (0.039)	0.007	0.02	910**	-0.029 (0.041)	0.48	0.6	912	0.031 (0.034)	0.36	0.59
Meta-analysis	22,492	-0.076 (0.009)	$1.00x10^{-17}$	$2.09x10^{-20}$	20,786	-0.011 (0.009)	0.23	0.22	13,900	0.024 (0.010)	0.013	0.020
AUC (area under the curve) insulin/ glucose (pmol/mmol) [2]												
AMISH	643	-0.0078 (0.037)	0.92	0.46	505	0.050 (0.036)	0.49	0.3	645	-0.0076 (0.026)	0.89	0.77
Botnia PPP	4,277	-0.050 (0.012)	3.1×10^{-5}	1.6×10^{-6}	2,811	-0.039 (0.018)	0.031	0.065	4,153***	0.0080 (0.011)	0.46	0.47
DIAGEN	950	0.039(0.026)	0.14	0.11	930	0.026 (0.028)	0.35	0.45	-	-	-	-
Ely	1,196*	-0.069 (0.023)	3.0×10^{-3}	2.6×10^{-4}	1,245	0.007 (0.020)	0.74	0.38	-	-	-	-
French Family members	272	-0.12 (0.084)	0.14	0.15	266	0 (0.095)	0.97	0.82	250	-0.020 (0.085)	0.84	0.86
French Haguenau	1,159	0.0090 (0.024)	0.71	0.7	1,159	0.032 (0.024)	0.17	0.49	1,173	0.022 (0.020)	0.27	0.31
French Obese Adults	237	-0.057 (0.093)	0.54	0.45	-	-	-	-	-	-	-	-
Hertfordshire	992**	-0.045 (0.030)	0.14	0.13	973	-0.046 (0.027)	0.084	0.2	-	-	-	-
Inter99	4,946	-0.10 (0.022)	4.7×10^{-6}	2.6×10^{-5}	4,984	-0.027 (0.020)	0.18	0.36	4,941	0.0080 (0.018)	0.66	1
METSIM	5,031	-0.038 (0.012)	2.1×10^{-3}	2.2×10^{-4}	5,066	-0.016 (0.014)	0.25	0.45	-	-	-	-
RISC	1,007	-0.073 (0.025)	4.1×10^{-3}	7.0×10^{-4}	1,004	0.0004 (0.024)	0.99	0.75	997	-0.017 (0.020)	0.42	0.32
ROCHE	571	-0.040 (0.038)	0.29	0.1	576	0.010 (0.036)	0.78	0.72	576	-0.048 (0.031)	0.12	0.31
ULSAM	928	-0.094 (0.025)	1.6×10^{-4}	1.4×10^{-3}	916**	-0.0002 (0.026)	0.99	0.81	918	-0.032 (0.022)	0.14	0.047
Meta-analysis	22,209	-0.051 (0.006)	$1.3x10^{-16}$	$3.7x10^{-20}$	20,435	0.010 (0.007)	0.16	0.19	13,653	-0.001 (0.007)	0.86	0.76
2h insulin (adjusted for 2h glucose) [3]												
AMISH	685	0.139 (0.045)	0.13	0.24	534**	0.17 (0.055)	0.13	0.091	688	-0.12 (0.033)	0.16	0.12
BLSA	460	-0.085 (0.056)	0.14	0.10	460	-0.006 (0.053)	0.91	0.93	460	-0.043 (0.042)	0.32	0.38
BotniaPPP	2,725	-0.067 (0.030)	0.028	0.013	2,699**	-0.11 (0.036)	$3.0x10^{-3}$	$3.06x10^{-3}$	4214***	-0.012 (0.013)	0.38	0.35
CHS-1	1,658	-0.081 (0.029)	$4.43x10^{-3}$	$3.08x10^{-3}$	1,658	-0.028 (0.025)	0.27	0.51	1,658	-0.065 (0.024)	$5.55x10^{-3}$	0.022
CHS-2	2,786	-0.060 (0.020)	$2.90x10^{-3}$	$1.60x10^{-3}$	-	-	-	-	-	-	-	-
DGI	-	-	-	-	1,045	-0.015 (0.057)	0.80	0.78	1,045	-0.033 (0.043)	0.45	0.58
DIAGEN	954	-0.062 (0.031)	0.047	0.041	934**	0.020 (0.033)	0.55	0.60	-	-	-	-
Ely	1,357*	-0.027 (0.024)	0.26	0.035	1,411	-0.0038 (0.021)	0.86	0.19	-	-	-	-
FHS	2,637	-0.055 (0.015)	$3.08x10^{-4}$	$3.79x10^{-5}$	2,618	-0.016 (0.014)	0.28	0.21	2,637	-0.012 (0.012)	0.32	0.21
FUSION	581	-0.026 (0.039)	0.51	0.57	581	-0.043 (0.041)	0.30	0.24	581	-0.059 (0.032)	0.066	0.043
Fusion Stage 2	286	-0.024 (0.046)	0.60	0.89	271	0.025 (0.055)	0.66	0.83	-	-	-	-
Hertfordshire	1071*	-0.073 (0.038)	0.05	0.046	1,048	-0.037 (0.033)	0.26	0.31	-	-	-	-
Inter99	5,349	-0.034 (0.016)	0.036	0.024	5,388	-0.059 (0.015)	$9.86x10^{-5}$	$5.96x10^{-4}$	5,342	-0.048 (0.014)	$4.19x10^{-4}$	$9.38x10^{-5}$
METSIM	5,055	-0.020 (0.015)	0.18	0.037	5,094**	-0.053 (0.017)	$1.80x10^{-3}$	$2.89x10^{-3}$	-	-	-	-
NHANES	528	-0.091 (0.040)	0.021	0.011	525	-0.080 (0.039)	0.039	0.043	528	-0.029 (0.033)	0.82	0.31
RISC	1,141	-0.036 (0.034)	0.24	0.11	1,136	-0.010 (0.032)	0.56	0.49	1,123	-0.057 (0.028)	0.041	0.023
ROCHE	583	-0.084 (0.049)	0.086	0.047	588	0.036 (0.046)	0.44	0.47	588	-0.091 (0.039)	0.021	0.029
Sorbs	-	-	-	-	651	-0.068 (0.048)	0.17	0.19	651	-0.029 (0.037)	0.46	0.59
ULSAM	937	-0.064 (0.029)	0.028	0.046	925**	-0.032 (0.030)	0.29	0.55	927	-0.086 (0.025)	$7.32x10^{-4}$	$1.75x10^{-4}$
Whitehall	3,411	-0.042 (0.019)	0.025	$2.27x10^{-3}$	3,421	-0.023 (0.017)	0.16	0.19	3,400	-0.033 (0.015)	0.028	0.041
Meta-analysis	32,204	-0.044 (0.006)	$1.99x10^{-13}$	$3.67x10^{-16}$	30,987	-0.029 (0.006)	$1.43x10^{-6}$	$3.09x10^{-6}$	23,842	-0.037 (0.006)	$7.45x10^{-11}$	$2.58x10^{-10}$

*rs11672660 proxy for *GIPR* SNP; **rs11708067 proxy for ADCY5 SNP; ***rs10519116 proxy for VPS13C SNP

1- Additive effect of the risk allele on insulinogenic index using study specific adjustments (including gender and age) with and without BMI adjustment.

2- Additive effect on AUC (area under the curve) insulin/ glucose using study specific adjustments (including gender and age) with and without BMI adjustment.

3- Additive effect of risk alleles on 2h insulin (adjusted for 2h glucose) using study specific adjustments (including gender and age) with and without BMI adjustment.

All outcomes were transformed using the natural logarithm.

Supplementary Table 5. Meta-analysis of GIPR SNP rs10423928 association with acute insulin response (AIR) during an intravenous glucose tolerance test (IVGTT) and with the incretin effect in non-diabetic individuals from up to 4 studies

***GIPR* SNP rs10423928 A**						
Study sample	**Acute insulin response during an IVGTT [1]**					
	N	**Per allele effect (SE) pmol/L*min (BMI adj.)**			***P*-value (BMI adj.)**	***P*-value**
FUSION	562	0.070 (0.056)			0.21	0.28
Botnia	487	0.020 (0.023)			0.40	0.24
Denmark	198	0.064 (0.090)			0.48	0.78
EUGENE2-Kuopio	262	0.096 (0.105)			0.36	0.35
Meta-analysis	1509	0.032 (0.020)			0.12	0.10
	% Incretin Effect [2]					
Study sample	**N**	**TT**	**TA**	**AA**	***P*-value (BMI adj.)**	***P*-value**
Botnia	351	80.8 +/- 8.7	78.7 +/- 8.9	75.8 +/- 9.7	0.007	0.003
Denmark	198	85.3 +/- 10.6	82.2 +/- 15.3	86.9 +/- 6.2	0.18	0.16
EUGENE2-Kuopio	255	64.8 +/- 15.5	63.4 +/- 13.9	59.9 +/- 13.6	0.054	0.082
Meta-analysis	804				4.3×10^{-4}	3.6×10^{-4}

1-Acute insulin response calculated during an IVGTT. Association analyses for each study were performed as described in methods, and *P*-values were combined using a fixed effects, inverse variance meta-analysis. No evidence of heterogeneity was observed ($P_{heterogeneity}$=0.87)

2-The percent incretin effect was calculated using the formula 100% x (AUCins OGTT-AUCins IVGTT)/AUCins OGTT. % incretin effect data are uncorrected and untransformed mean values. Association analyses for each study were performed as described in methods, and P-values were combined using a fixed effects z-score based meta-analysis. No evidence of heterogeneity was observed ($P_{heterogeneity}$=0.86)

Supplementary Table 6. Association of *GIPR* rs10423928, *ADCY5* rs2877716 and *VPS13C* rs17271305 with type 2 diabetes (T2D) in up to 27 case-control studies

Study Sample	Ncases/ Ncontrols	***GIPR* rs10423928 A**		***ADCY5* rs2877716 C**		***VPS13C* rs17271305 G**	
		OR(95% CI)	*P* -value	OR(95% CI)	*P* -value	OR(95% CI)	*P* -value
58 BC_OxGN	654/1653	-	-	1.20 (1.02-1.41)#	0.030	-	-
ADDITION/ELY	837/1590	1.15 (0.97-1.36)*	0.11	1.31 (1.10-1.55)**	$1.89X10^{-3}$	-	
ARIC	696/6420	1.19 (0.99-1.44)	0.064	1.09 (0.95-1.26)	0.19	0.97 (0.86-1.10)	0.66
CCC	514/500	0.97 (0.77-1.23)*	0.83	1.32 (1.07-1.64)**	$9.69x10^{-3}$	-	-
Danish	3514/4906	1.19 (1.07-1.32)	0.0014	1.19 (1.08-1.32)	0.00059	0.91 (0.84-1.00)	0.052
DGDG	679/697	-	-	1.11 (0.92-1.35)	0.28	-	-
deCODE	1465/23194	-	-	1.07 (0.97-1.19)	0.17	-	-
DGI	1022/1075	-	-	1.01 (0.86-1.20)	0.89	1.04 (0.92-1.17)	0.59
DIAGEN	533/743	0.93 (0.77-1.14)	0.48	1.51 (1.22-1.87)**	$1.4x10^{-4}$	-	-
ERGO	1178/4761	-	-	1.08 (0.98-1.20)	0.13	-	-
EUROSPAN	268/3710	-	-	0.99 (0.79-1.25)	0.95	-	-
FHS	674/8338	0.91 (0.76-1.07)	0.26	1.09 (0.94-1.30)	0.26	1.02 (0.89-1.14)	0.81
French case-control	1107/1190	1.17 (0.91-1.49)	0.22	-	-	0.95 (0.77-1.17)	0.61
FUSION	1161/1174	1.02 (0.88-1.12)	0.84	1.06 (0.91-1.24)	0.44	0.91 (0.81-1.02)	0.12
FUSION stage 2	1180/1251	1.24 (1.09-1.41)	$1.4x10^{-3}$	1.10 (0.94-1.28)**	0.22	-	-
GCI Poland	790/803	0.97 (0.81-1.15)	0.70	-		1.06 (0.90-1.24)	0.51
GCI US	1010/987	0.99 (0.84-1.18)	0.95	0.94 (0.80-1.11)**	0.48	1.07 (0.93-1.23)	0.36
HPFS	1095/1241	-		0.97 (0.84-1.13)	0.71	0.85 (0.75-0.96)***	0.010
KORA	433/1438	-		1.14 (0.94-1.38)	0.18	-	-
MDC_MDR	2764/3185	1.10 (0.99-1.22)	0.065	1.20 (1.08-1.33)**	$4.6x10^{-4}$	-	-
METSIM	879/3582	0.99 (0.87-1.13)	0.85	1.24 (1.06-1.44)	$5.5x10^{-3}$	-	-
NHANES	286/1194	1.30 (1.03-1.63)	0.026	1.14 (0.90-1.45)	0.2903	1.26 (1.03-1.53)	0.027
NHS	1467/1754	-		1.18 (1.04-1.34)**	0.011	0.98 (0.88-1.10)***	0.77
Norfolk	2779/2271	1.04 (0.92-1.17)*	0.52	1.13 (1.05-1.22)**	$7.13x10^{-4}$	-	-
Roche	461/600	0.98 (0.77-1.25)	0.86	0.86 (0.69-1.08)	0.21	1.15 (0.95-1.41)	0.16
UKT2DGC	5113/6615	-		1.10 (1.04-1.18)#	$1.7x10^{-3}$	-	-
WTCCC	1924/2938	-		1.08 (0.97-1.19)	0.15	0.94 (0.86-1.02)	0.14
N cases/controls		19,091/38,508		35,869/89,798		15,180/32,556	
Meta-analysis (fixed effects)		**1.07 (1.03-1.12)**	**$1.8x10^{-4}$**	**1.12 (1.09-1.15)**	**$4.8x10^{-18}$**	**0.97 (0.94-1.00)**	**0.083**
I^2		39.3% (0-65.3%)		35.2% (0-59.3%)		48.7% (0-72.8%)	
Meta-analysis (random effects)		**1.07 (1.02-1.12)**	**$9.6x10^{-3}$**	**1.12 (1.08-1.16)**	**$9.4x10^{-11}$**	**0.99 (0.94-1.04)**	**0.62**

*rs11672660 proxy for *GIPR* SNP; **rs11708067proxy for ADCY5 SNP, #rs11717195 proxy for ADCY5 SNP;***rs12913951 proxy for VPS13C SNP

Note: Meta-analysis of GWAS from DGI, FUSION and WTCCC studies have been published by DIAGRAM (Zeggini et al, 2008).

SUPPLEMENTARY NOTE

Expression analyses

We used commercial cDNAs from the Human MTC panel I for lung, kidney, heart, muscle and liver (BD Biosciences Clontech) and RNAs that were reverse transcribed from the brain, small intestine and adipose tissue (Human Adult Normal 5 Donor Pool, BioChain Institute). Pancreatic islets and sorted beta cells were obtained from human adult brain-dead donors in accordance with the French regulations and the local institutional ethical committee, as previously described.[1] Briefly, pancreatic islets were isolated after ductal distension of the pancreata and digestion of the tissue with Liberase (Roche Diagnostics). Human beta cells were sorted by FACS analysis of semi-purified preparations of islet cells using Newport Green, a specific zinc-fluorescent probe.[1] Total RNA was extracted using Nucleospin RNA II kit (Macherey Nagel) according to the manufacturer's instructions. Samples were treated with DNase 1 (Ambion) to ensure residual genomic contamination was removed. cDNA samples were amplified by standard PCR using the Fast Start Taq (Roche Applied Science). For each sample, 1µg of total RNA was used to generate cDNA by random primed first strand synthesis (Applied Biosystems) according to manufacturer's protocol. Reverse transcription was also performed on beta cells samples in the absence of the enzyme, reverse transcriptase, and these samples used as negative controls. Resulting cDNA for each tissue was diluted 1:10 and 4µl used in a 20µl qRT-PCR reaction with 10µl gene expression mastermix (Applied Biosystems) and 1µl gene specific assay (Applied Biosystems).

Islet Microarrays for expression by genotype

Human islets at Lund University Diabetes Center (LUDC) were provided by the Nordic network for clinical islets transplantation by the courtesy of Dr. Olle Korsgren, Uppsala, Sweden. Total RNA was isolated with the AllPrep DNA/RNA Mini Kit (Qiagen GmbH, Hilden, Germany). RNA quality and concentration were measured using an Agilent 2100 bioanalyzer and Nanodrop ND-1000 equipment, respectively. The microarrays were performed following the Affymetrix standard protocol. Briefly, 100-300 ng total RNA was processed following the GeneChip® Expression 3'-Amplification Reagents One-cycle cDNA synthesis kit instructions (Affymetrix Inc, Santa Clara, CA, USA) to produce double-stranded cDNA. This was used as a template to generate biotin-targeted cRNA following manufacturer's specifications. 15 µ g of the biotin labeled cRNA was fragmented to strands between 35 and 200 bases in length, 10 µg of which was hybridized onto the GeneChip® Human Gene 1.0 ST whole transcript based assay overnight in the GeneChip® Hybridization oven 6400 using standard procedures. The arrays were washed and stained in a GeneChip® Fluidics Station 450. Scanning was carried out with the GeneChip® Scanner 3000 and image analysis was performed using GeneChip® Operating Software. The array data were summarized and normalized with Robust Multi-array Analysis (RMA) method using the software "Expression Console" (Affymetrix).

In up to 20 samples, no association was observed between genotypes at rs10423928 and *GIPR*, *EML2* or *SNRPD2* transcripts (*P*= 0.76, 0.56 and 0.36 respectively), or between genotypes at rs2877716 and the *ADCY5* or SEC22A transcripts (*P*= 0.86 and 0.79 respectively), or between genotypes at rs17271305 and FAM148A transcript (*P*= 0.90). A probe to assay VPS13C gene expression was not present on the microarray.

T2D Association Studies

SNPs from three loci (*GIPR*, *ADCY5* and/or *VPS13C*) were genotyped in previously described T2D case-control studies (58BC_OxGN, Addition/ELY, CCC, DIAGEN, French case-

Nature Genetics: doi:10.1038/ng.521

control, FUSION stage 2, GCI Poland, GCI US, MDC_MDR, METSIM, Norfolk Diabetes case-control study, Roche and UKT2DGC). Summary association results for tested SNPs were also obtained from a) published GWAS meta-analysis of the DIAGRAM consortium[39] or unpublished GWAS meta-analyses of the DIAGRAM+ consortium (comprising DGDG, DGI, ERGO, EUROSPAN, FUSION, KORA, WTCCC and deCODE), b) unpublished GWAS from the NHS and HPFS studies, and c) GWAS of cohort studies with prevalent cases at baseline (ARIC, FHS). Association of SNPs at the *GIPR*, *VPS13C* and *ADCY5* loci was tested using an additive genetic model, adjusted for study-specific covariates. Genotyped SNPs with a call rate >90%, MAF > 1% and HWE P-value > 10^{-4} were included for analysis, and imputed SNPs were only accepted if r^2hat>0.3 (MACH) or SNP Info > 0.4 (IMPUTE). Results were combined using an inverse variance meta-analysis assuming fixed effects. Heterogeneity was assessed using the I^2 statistic, and as estimates were over 25%, we performed a second meta-analysis assuming random effects. Future prediction of type 2 diabetes was performed in the Malmo Preventive Project. Analysis details and references for each T2D study are provided below.

ARIC: Details of theAtherosclerosis Risk in Communities (ARIC) Study scan and samples have been described previously.[2] In brief, the analysis included 696 T2D cases and 6420 non-cases ascertained at the baseline examination (1987-89). Diabetes was defined as self-reported physician diagnosis of diabetes, self-reported use of diabetes medications in the last two weeks, fasting glucose >= 126 mg/dL, or casual glucose >= 200 mg/dL. Non-cases had fasting glucose < 110 mg/dL. Samples were genotyping using the Affymetrix Genome-Wide Human 6.0 array. The MACH software (v1.0.16) was used to impute untyped or partially typed SNPs. A total of 708,116 directly genotyped SNPs and 1,849,116 imputed SNPs passed QC. ProbABEL software was used to analyze the SNPs by logistic regression assuming an additive model and adjusting for age, gender, field center, and BMI.

DGDG: The Diabetes Gene Discovery Group scan and samples have been described previously.[3] In brief, 690 non-obese (Body-mass Index (BMI) <30), family history positive Type 2 Diabetics (T2D) and 730 controls (selected among participants in a longitudinal study (DESIR) 2: healthy subjects with age at exam >45 years and BMI <27) were genotyped for 309,385 autosomal SNPs that passed QC on the Illumnia Human Hap300 BeadArray. Genotypes for untyped SNPs were imputed using the IMPUTE software package, of which 2,139,197 SNPs passed imputation QC. 2,557,287 genotyped and imputed SNPs were analyzed by logistic regression assuming an additive model, using the SNPTEST software package. The analysis was adjusted using genomic control: 1.10 for directly genotyped SNPs and 1.098 for imputed SNPs. The results for the *ADCY5* SNP rs2877716 were extracted for this manuscript.

deCODE: Details of the previous scan and samples have been described previously.[4,5] In brief, a collection of Icelandic samples consisting of 1,465 T2D cases and 23,194 population controls were genotyped for 281,410 autosomal SNPs that passed QC on either the Illumina HumanHap300/300-duo+ or CNV370-duo Bead Arrays. Genotypes for untyped SNPs were imputed using the IMPUTE software package, of which 2,056,955 SNPs passed imputation QC. 2,338,365 genotyped and imputed SNPs were analyzed by logistic regression assuming an additive model, using the SNPTEST software package. The analysis was adjusted using genomic control: 1.308 for directly genotyped SNPs and 1.305 for imputed SNPs. The magnitude of the adjustment factor is primarily due to the relatedness of the Icelandic cases and controls.

Nature Genetics: doi:10.1038/ng.521

DGI: Details of the previous scan and samples have been described previously[6,7], with one modification. Unlike the previous meta-analysis, we excluded the discordant sibship component because calculation of effect size and uncertainty around that estimate has not been previously determined.

DGI Stage 2 (MDC_MDR, GCI Poland, GCI US,): Clinical characteristics of the samples have been described previously[6,7]. All three SNPs were genotyped using the iPLEX Sequenom MassArray platform (http://www.sequenom.com/Assets/pdfs/appnotes/8876-006.pdf) and analyzed for association with T2D using chi-square analysis.

Malmo Diabetes Registry/Malmo Diet and Cancer Study: The Sweden case control sample consisted of 2,764 cases from the Malmo Diabetes Registry and 3,185 normoglycemic controls from the Malmo Diet and Cancer study. Cases had age of onset >35 years, C-peptide >0.3 nmol/L and were GAD Ab negative, and were frequency matched to controls by age, sex and BMI.

GCI-US sample: The US case-control sample comprised 1,010 cases of European ancestry from the United States matched to 987 control subjects by age, sex, and grandparental country of origin.

GCI-Poland sample. The Poland case-control sample consisted of 790 diabetic cases and 803 control subjects, matched individually by age and sex.

DANISH Case-Control Study: The prioritized polymorphisms were genotyped in 8632 Danes comprising the population-based Inter99 sample of middle-aged people sampled at Research Centre for Prevention and Health[8], type 2 diabetic patients sampled through the out-patient clinic at Steno Diabetes Center, a population-based group of middle-aged glucose-tolerant subjects recruited from Steno Diabetes Center, and screen detected type 2 patients sampled in Danish part of the ADDITION study sampled by Department of General Practice at University of Aarhus.[9] Detailed characteristics of study populations have been described.[10] In total, 3589 type 2 diabetic patients and 5043 glucose-tolerant control subjects were genotyped using Taqman allelic discrimination (KBioscience, Herts, UK).

DIAGEN: Subjects from German families with a family history of type 2 diabetes, obesity, or dyslipoproteinaemia were investigated as described elsewhere.[11] All subjects were from the city of Dresden and adjoining areas. Exclusion criteria were: known diabetes mellitus, severe renal disease, disease with a strong impact on life expectancy, and therapy with drugs known to influence glucose tolerance (thiazide diuretics, beta blockers, steroids). All individuals underwent a 75g oral glucose tolerance test following an overnight period of fasting (10 hours minimum) with measurements of plasma glucose, insulin, and free fatty acids (NEFA) at fasting and at 30, 60, 90 and 120 minutes after glucose challenge. After a three-year period, some subjects again underwent an oral glucose tolerance test using the same protocol. The cohort was divided into three glucose tolerance groups according to the results of the baseline and follow-up oGTT: normoglycaemic (NGT), impaired glucose tolerance (IGT) including those with impaired fasting glucose (IFG), and type 2 diabetes mellitus based on the WHO/ADA criteria of 1997/1999. As patients underwent oGTT analyses both at inclusion and following the three-year interim, five groups were defined according to the evolution of their diabetic status: those whose disease status remained unchanged as NGT, IGT/IFG and type 2 diabetes, those presenting a regression and those presenting a progression of the disease. Genotyping was performed on 533 T2D cases and 743 controls using Sequenom iPLEX Gold SBE assays at the

Nature Genetics: doi:10.1038/ng.521

National Human Genome Research Institute. SNPs were analyzed using logistic regression with adjustment for sex and an additive model for the genetic effect.

EUROSPAN: In brief, 268 T2D cases and 3,710 controls sampled across 4 genetically isolated populations throughout Europe were genotyped for approximately 288,389 (plus an additional 21,261) SNPs on either the Illumina HumanHap300 or HapMap 370CNV. Genotypes for untyped or partially genotyped SNPs were imputed using the MACH1 software package, of which 2,058,605 passed imputation QC. 2,368,255 SNPs genotyped and imputed SNPs were analyzed using logistic regression assuming an additive model, including covariates for sex and ascertainment province, using the ProbABEL and GenABEL software packages.

Framingham Heart Study (FHS) SNP-Health Association Resource (SHARe): The analysis included 674 cases and 7664 controls from all three generations of Framingham participants. Diabetes was defined as: 1) Cohort (Gen 1): casual glucose ≥200 mg/dl at any exam 1-22 or taking diabetes medication (oral or insulin) at any exam 2) Offspring (Gen 2): Fasting plasma glucose ≥126 mg/dl at any exam 1-7 or diabetes treatment at any exam. In the Offspring, >99% of diabetes is type 2 diabetes. 3) Gen 3: Fasting ≥ 8 hours and fasting plasma glucose ≥126 mg/dl at exam 1 or diabetes treatment at exam 1

Samples were genotyped using the Affymetrix 500K and MIPS 50K SNPs. The MACH (version 1.0.15) software was used to impute 2,543,887 ungenotyped SNPs, 2,411,590 of SNPs passed QC criteria. A total of 2,438,639 directly genotyped and imputed SNPs were analyzed using the logistic regression model using a robust variance estimated via generalized estimating equations with each pedigree as a cluster. Covariates included in the model included, sex, cohort indicator and sex x cohort interaction term. For imputed SNPs, the expected number of alleles (dosage) was used in the analysis. The genomic control lambda was estimated as 1.04 for directly genotyped SNPs and 1.02 for imputed results.

French case-control: T2D cases were recruited at the Endocrinology-Diabetology Department of the Corbeil-Essonnes Hospital. Details about these cases are provided elsewhere.[3] Controls were DESIR participants with FPG < 6.1 mmol/l and no current T2D treatment. Individuals with birth place outside metropolitan France and/or with non-European ancestry were excluded after population structure analyses as previously described.[12]

FUSION: Details of the previous scan and samples have been described elsewhere.[7,13] In brief, the FUSION stage 1 samples consisting of 1,161 Finnish T2D cases and 1,174 Finnish normal glucose tolerant controls approximately frequency matched to cases based on 5-year age category, sex, and birth province were genotyped for 306,244 autosomal SNPs that passed QC using the Illumina HumanHap300 BeadChip (version 1.1). Genotypes for untyped SNPs were imputed using the MACH1 software package, of which 2,106,846 passed imputation QC. 2,413,090 genotyped and imputed SNPs were analyzed using logistic regression assuming an additive model, including covariates for sex, 5-year age category, and birth province. To account for uncertainty in the imputation of untyped SNPs, imputed SNPs were represented by the expected allele count. The analysis was adjusted using genomic control: 1.03 for directly genotyped SNPs and 1.04 for imputed SNPs.

FUSION stage 2: The FUSION study stage 2 sample includes 1211 T2D cases and 1266 NGT controls selected from the Dehko 2D, Health 2000, Finrisk 1987, Finrisk 2002, Savitaipale Diabetes, and Action LADA studies.[13] FUSION stage 2 samples do not overlap with the

Nature Genetics: doi:10.1038/ng.521

individuals used in the FUSION GWAS. Genotyping was performed using Sequenom iPLEX Gold SBE assays at the National Human Genome Research Institute. SNPs were analyzed using logistic regression with adjustment for sex, 5-year age category and birth province and an additive model for the genetic effect.

GEM (CCC, ADDITION-Ely, Norfolk Diabetes Case-Control Study):

Cambridgeshire case–control study: The Cambridgeshire case–control study is a population based study of type 2 diabetes (T2D) cases, aged 45-76 years, and age and sex matched controls. Cases were randomly selected from general practitioner diabetes registers in Cambridgeshire, UK, and T2D was defined as onset of diabetes after the age of 30 years and without insulin use in the first year after diagnosis.[14] Controls were recruited at random from the same population sampling frames, and individually matched to cases for age, sex and GP practice. Diabetes was excluded in controls by medical record search and by a glycated haemoglobin measurement of less than 6%. The study received ethical approval from the Cambridge Local Research Ethics Committee, and participants provided informed consent. In the current analyses, we include 544 cases and 527 controls, representing all white Europeans who had DNA available and information on body mass index.

ADDITION-Ely case-control study: Previously undiagnosed prevalent cases of T2D, defined using WHO OGTT criteria, were identified via a population-based stepwise screening strategy among 40 to 69 year olds participating in the UK Cambridge arm of the ADDITION study. Current analyses include 799 white European men and women who had DNA available and information on body mass index.[9] Controls were identified from the MRC Ely study, a population-based cohort of white European men and women aged 35 to 79 years without diagnosed diabetes and from a similar sampling frame as the cases.[15] Based on WHO OGTT criteria, participants were confirmed as controls (n=1,606) or classified as cases (n=92). The Cambridge Research Ethics Committee approved both studies.

Norfolk Diabetes case-control study: The Norfolk Diabetes Case-Control Study is an ongoing study of white European men and women with T2D patients in Norfolk. All T2D patients identified through general practice diabetes registers in Norfolk and local hospital diabetes clinic and retinal screening programme patient registers are invited to participate; a total of 2,908 white European cases were included in the current analyses. Participants with insulin use during the first year of diagnosis, and those with cystic fibrosis, chronic pancreatitis or long term steroid use were excluded from the study. 2,394 controls free of known diabetes at baseline or during follow-up were randomly selected from EPIC-Norfolk participants. The Norfolk study was approved by the Norwich Local Research Ethics Committee.

Genotyping was performed at the MRC Epidemiology Unit using custom TaqMan® SNP assays (Applied Biosystems, Warrington, UK), with 10ng of genomic DNA. The call frequency of genotyped samples was >95% and HWE p-values >0.1. Between 2-4% duplicate samples were used per study and these were 97-100% concordant. Associations between each SNP and diabetes were tested using logistic regression analyses, assuming an additive genetic model and adjusting for age, sex and BMI.

HPFS: Details of the Health Professionals Follow-up Study (HPFS) cohorts have been described previously.[16] The cases and controls for the HPFS Type 2 Diabetes (T2D) project were selected among those with a blood sample (N=18,159) using a "nested" case-control study design. Cases of T2D were identified by self-report on biennial follow-up questionnaires and confirmed by a medical record-validated supplementary questionnaire.[17] Controls were defined as those free of

Nature Genetics: doi:10.1038/ng.521

diabetes at the time of diagnosis of the case. Genotyping was performed using the Affymetrix Genome-Wide Human 6.0 array. 742,032 SNPs passed QC in 1,146 T2D cases and 1,241 controls who were of European ancestry. We used PLINK software to analyze the association by logistic regression assuming an additive model.

KORA T2D study: Details of the previous scan and samples have been described previously.[18,19] In brief, 433 T2D cases and1,438 nondiabetic control participants of the KORA (Cooperative Health Research in the Region of Augsburg / Kooperative Gesundheitsforschung in der Region Augsburg) surveys S3 (1994/1995), F3 (follow-up of S3, 2004/2005), and S4 (1999-2001) were genotyped for 356,183 autosomal SNPs that passed QC using the Affymetrix GeneChip Human Mapping 500k Array Set. Genotypes for untyped SNPs were imputed using the IMPUTE software package (version 0.3.2) of which 1,969,049 SNPs passed imputation QC. 2,325,232 directly genotyped and imputed SNPs were analyzed by logistic regression assuming an additive model including covariates for age and sex using the SNPTEST software package. The analysis was adjusted using genomic control: 1.04 for both directly genotyped and imputed SNPs.

Malmö Preventive Project (MPP): In this large population based prospective study from the city of Malmö, Sweden, we included 16,061 non-diabetic subjects, 2,063 of whom developed T2D during a 24.8 year median follow-up period.[20,21] Diagnosis of diabetes was confirmed from patient records or based upon a fasting plasma glucose ≥7.0 mmol/l. We investigated the predictive ability of *ADCY5* (rs2877716) polymorphisms for future type 2 diabetes using logistic-regression analysis adjusted for age and secondary age and BMI. Since men and women were included at different times, we adjusted for this factor using the participation period (coded 0 or 1), sex, and an interaction term (participation period × sex, which was coded 0 or 1) as covariates in the analyses.

Metabolic Syndrome in Men (METSIM): The METSIM study of men randomly sampled from the town of Kuopio in Eastern Finland (population 95.000) has been described previously.[22] Our sample included 879 T2D cases and 3582 NGT controls, aged 45-72 years. Genotyping was performed using iPLEX Gold SBE assays at the National Human Genome Research Institute. We performed logistic regression adjusted for 5-year age category using an additive genetic model.

NHS: Details of the Nurses' Health Study (NHS) cohorts have been described previously.[23] The cases and controls for the NHS Type 2 Diabetes (T2D) project were selected among those with a blood sample (N=32,826) using a "nested" case-control study design. Cases of T2D were identified by self-report on biennial follow-up questionnaires and confirmed by a medical record-validated supplementary questionnaire.[17] Controls were defined as those free of diabetes at the time of diagnosis of the case. Genotyping was performed using the Affymetrix Genome-Wide Human 6.0 array. 706,896 SNPs passed QC in 1,532 T2D cases and 1,754 controls who were of European ancestry. We used PLINK software to analyze the association by logistic regression assuming an additive model.

Roche Study: Details of the sample have been previously described.[24] Patients with diabetes mellitus and non-diabetic control subjects, with no personal history or family history of diabetes in first degree relatives and with normal (<6.1 mmol/l or 110 mg/dl) fasting glucose levels, were recruited and evaluated by the Diabetes Center, Massachusetts General Hospital and the Division of Endocrinology and Metabolism, Brigham and Women's Hospital as part of an observational study of diabetic and pre-diabetic subjects. All SNPs were genotyped using allele-

Nature Genetics: doi:10.1038/ng.521

specific primer extension of multiplex amplified products with detection by matrix-assisted laser desorption ionization–time of flight mass spectroscopy on an iPLEX Sequenom platform. Genotyping call rates were 99% on average, and the average consensus rate based on 254 duplicate samples was 99%. Association analysis was performed using an additive genetic model.

The Rotterdam Study (ERGO): In brief, 1,178 T2D cases and 4,761 controls were genotyped for 500,264 SNPs that passed QC using the Infinium II assay on the HumanHap550 Genotyping BeadChips (Illumina Inc., San Diego, CA, USA). Genotypes for untyped SNPs were imputed using the MACH1 software package, of which 2,067,878 were imputed. 2,568,142 directly genotyped and imputed SNPs were analyzed using logistic regression assuming an additive model, using the ProbABEL and GenABEL software packages. The analysis was adjusted using genomic control: 1.0064 for directly genotyped SNPs and 1.01 for imputed SNPs.

WTCCC: Details of the previous scan and samples have been described previously.[7] In brief, the WTCCC/UKT2D stage 1 UK samples consisting of 1,924 T2D cases and 2,938 population controls were genotyped for 393,143 autosomal SNPs that passed QC using the Affymetrix GeneChip Human Mapping 500k Array Set. Genotypes for untyped SNPs were imputed using the IMPUTE software package, of which 1,915,393 SNPs passed imputation QC. 2,308,535 directly genotyped and imputed SNPs were analyzed by logistic regression assuming an additive model including two ancestry informative principal components covariates to correct for population structure, using the SNPTEST software package. The analysis was adjusted using genomic control: 1.06 for directly genotyped SNPs and 1.08 for imputed SNPs.

UK Type 2 Diabetes Genetics Consortium (UKT2DGC) collection and OxGN/58BC (UKRS2): These samples represent an expansion of the "UK Stage 2" samples described previously.[7,25] The UKT2DGC ("Dundee") collection study sample of 5113 T2D cases and 6615 controls includes subjects previously described[7] as RS1 and RS3, together with added tranches of cases and controls ascertained more recently. Since all 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 diabetesspecific 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[7,26] 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).

Nature Genetics: doi:10.1038/ng.521

ACKNOWLEDGEMENTS

Replication genotyping was supported in part by Diabetes UK grant RD08/0003704.

1958 Birth Cohort/ UKRS2: For the 1958 Birth Cohort, venous blood collection was funded by the UK Medical Research Council and cell-line production, DNA extraction and processing by the Juvenile Diabetes Research Foundation and the Wellcome Trust. We acknowledge use of genotype data from the British 1958 Birth Cohort DNA collection, funded by the Medical Research Council grant G0000934 and the Wellcome Trust grant 068545/Z/02. 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.

Amish: The Amish research studies were supported by the National Institutes of Health (NIH) research grant R01 DK54261 and U01 HL72515, Baltimore Diabetes Research and Training Center, Grant P60 DK079637, the University of Maryland General Clinical Research Center, Grant P30 DK072488, Clinical Nutrition Unit of Maryland, Grant M01 RR 16500, the Johns Hopkins University General Clinical Research Center, Grant M01 RR 000052, General Clinical Research Centers Program, National Center for Research Resources (NCRR), NIH, the Baltimore Veterans Administration Geriatric Research and Education Clinical Center (GRECC), American Diabetes Association and GlaxoSmithKline. We gratefully acknowledge the Amish liaisons, fieldworkers, and the extraordinary cooperation and support of the Amish Community, without whom these studies would not be possible.

The Atherosclerosis Risk in Communities Study is carried out as a collaborative study supported by National Heart, Lung, and Blood Institute contracts N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, N01-HC-55022, R01HL087641, R01HL59367 and R01HL086694; National Human Genome Research Institute contract U01HG004402; and National Institutes of Health contract HHSN268200625226C. The authors thank the staff and participants of the ARIC study for their important contributions. Infrastructure was partly supported by Grant Number UL1RR025005, a component of the National Institutes of Health and NIH Roadmap for Medical Research.

BLSA: The BLSA was supported in part by the Intramural Research Program of the NIH, National Institute on Aging. A portion of the support was through a R&D contract with MedStar Research Institute.

CHS: The CHS research reported in this article was supported by contract numbers N01-HC-85079 through N01-HC-85086, N01-HC-35129, N01 HC-15103, N01 HC-55222, N01-HC-75150, N01-HC-45133, grant numbers U01 HL080295 and R01 HL087652 from the National Heart, Lung, and Blood Institute, with additional contribution from the National Institute of Neurological Disorders and Stroke. A full list of principal CHS investigators and institutions can be found at http://www.chs-nhlbi.org/pi.htm. DNA handling and genotyping was supported in part by National Center for Research Resources grant M01RR00069 to the Cedars-Sinai General Clinical Research Center Genotyping core and National Institute of Diabetes and Digestive and Kidney Diseases grant DK063491 to the Southern California Diabetes Endocrinology Research Center.

CoLaus: The CoLaus study was supported by research grants from GlaxoSmithKline, from the Swiss National Science Foundation (Grant number 33CSO-122661) and from the Faculty of

Nature Genetics: doi:10.1038/ng.521

Biology and Medicine of Lausanne, Switzerland. We thank Yolande Barreau, Mathieu Firmann, Vladimir Mayor, Anne-Lise Bastian, Binasa Ramic, Martine Moranville, Martine Baumer, Marcy Sagette, Jeanne Ecoffey and Sylvie Mermoud for data collection. Finally we would like to express our gratitude to all the participants.

deCODE: We thank the Icelandic study participants whose contribution made this work possible. We would also like to acknowledge the staff at the Clinical Research Centre (Iceland) and the deCODE Genetics biological materials and genotyping facilities for their work. The research performed at deCODE Genetics was part funded through the European Community's Seventh Framework Programme (FP7/2007-2013), ENGAGE project, grant agreement HEALTH-F4-2007-201413.

DGI and BotniaPPP: We thank 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. L.G., T.Tu., V.L., B.I. and the Botnia Study are principally supported by The Folkhalsan Research Foundation, Sigrid Juselius Foundation, Finnish Cultural Foundation, The Ministry of Education in Finland, the Finnish Diabetes Research Foundation, Ollqvist Foundation and Clinical Research Institute HUCH Ltd; work in Malmö, Sweden was also funded by grants from the Swedish Research Council and the Wallenberg Foundation.

DIAGEN: We are grateful to all of the patients who cooperated in this study and to their referring physicians and diabetologists in Saxony. This study was supported by the Dresden University of Technology funding grant, Med Drive. EFS: MNW is a Vandervell Foundation Research Fellow.

Fenland: The Fenland Study is funded by the Wellcome Trust and the Medical Research Council. We are grateful to all the volunteers for their time and help, and to the General Practitioners and practice staff for help with recruitment. We thank the Fenland Study coordination team and the Field Epidemiology team of the MRC Epidemiology Unit for recruitment and clinical testing. We also thank the NIHR Cambridge Biomedical Research Centre, Cambridge, U.K. for biochemical analyses.

Framingham Heart Study: This research was conducted in part using data and resources from the Framingham Heart Study of the National Heart Lung and Blood Institute of the National Institutes of Health and Boston University School of Medicine. The analyses reflect intellectual input and resource development from the Framingham Heart Study investigators participating in the SNP Health Association Resource (SHARe) project. This work was partially supported by the National Heart, Lung and Blood Institute's Framingham Heart Study (Contract No. N01-HC-25195) and its contract with Affymetrix, Inc for genotyping services (Contract No. N02-HL-6-4278). A portion of this research utilized the Linux Cluster for Genetic Analysis (LinGA-II) funded by the Robert Dawson Evans Endowment of the Department of Medicine at Boston University School of Medicine and Boston Medical Center. The study is also supported by National Institute for Diabetes and Digestive and Kidney Diseases (NIDDK) R01 DK078616 to Drs. Meigs, Dupuis and Florez, NIDDK K24 DK080140 to Dr. Meigs, and NIDDK Research Career Award K23 DK65978,

a Massachusetts General Hospital Physician Scientist Development Award and a Doris Duke Charitable Foundation Clinical Scientist Development Award to Dr. Florez.

French GWA and replication studies were supported in part by the "Conseil Regional Nord-Pas-de-Calais: Fonds européen de développement économique et regional", Genome Quebec-Genome Canada and the British Medical Research Council. NB-N's position is supported by a grant from the ANR (Agence Nationale pour la Recherche: ANR-06 PHYSIO - 037 -02). We acknowledge funding to PF by the European Union (Integrated Project EURODIA LSHM-CT-2006-518153 in the Framework Programme 6 [FP06] of the European-Community). We thank J Weill for part of the obesity families recruitement, M Deweirder and F Allegaert for DNA extraction, S Daghmoun and C Traband from the Haguenau study, S Gaget, Y Labrune, S Gallina and F De Graeve for bioinformatical and statistical support.

FUSION: We would like to thank the many Finnish volunteers who generously participated in the FUSION, D2D, Health 2000, Finrisk 1987, Finrisk 2002, and Savitaipale studies from which we chose our FUSION GWA and replication cohorts. We also thank Terry Gliedt and Peggy White for informatics and analysis support. The Center for Inherited Disease Research performed the 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.Boe.), and DK072193 (K.L.M.). Additional support comes from the National Human Genome Research Institute intramural project number 1 Z01 HG000024 (F.S.C.).

GEM Consortium: IB acknowledges support from WT grant 077016/Z/05/Z and EU FP6 funding (contract no.LSHM-CT-2003-503041). We thank all study participants. The work on the Cambridgeshire case-control, Ely, ADDITION and EPIC-Norfolk studies was funded by support from the Wellcome Trust and MRC. The Norfolk Diabetes study is funded by the MRC with support from NHS Research & Development and the Wellcome Trust and we are grateful to the study team. We thank Dr Simon Griffin, MRC Epidemiology Unit, for assistance with the ADDITION study and the technical teams at the MRC Epidemiology laboratory for genotyping and informatics support.

The Hertfordshire Cohort Study was funded by the Medical Research Council and Arthritis Research Campaign. Genotyping is supported by an MRC-GSK grant to the MRC Epidemiology Unit, Cambridge, UK.

Inter99 and ADDITION Study Denmark: The Inter99 was initiated by: Torben Jørgensen (PI), Knut Borch-Johnsen (co-PI), Hans Ibsen and Troels F. Thomsen. The steering committee comprises the former two and Charlotta Pisinger. The study was financially supported by research grants from the Danish Research Council, The Danish Centre for Health Technology Assessment, Novo Nordisk Inc., Research Foundation of Copenhagen County, Ministry of Internal Affaires and Health, The Danish Heart Foundation, The Danish Pharmaceutical Association, The Augustinus Foundation, The Ib Henriksen Foundation, the Becket Foundation, the Lundbeck Foundation Centre of Applied Medical Genomics for Personalized Disease Prediction, Prevention and Care (LUCAMP), and the Danish Diabetes Association. The ADDITION study Denmark was supported by the National Health Services in the counties of Copenhagen, Aarhus, Ringkøbing, Ribe and South Jutland, together with the Danish Research Foundation for General Practice, Danish Centre for Evaluation and Health Technology Assessment, the diabetes fund of the National Board of Health, the Danish Medical Research Council, the Aarhus

Nature Genetics: doi:10.1038/ng.521

University Research Foundation and the Novo Nordisk Foundation. The study received unrestricted grants from Novo Nordisk, Novo Nordisk Scandinavia, Astra Denmark, Pfizer Denmark, GlaxoSmithKline Pharma Denmark, Servier Denmark and HemoCue Denmark.

KORA: Studies were financed by the Helmholtz Zentrum München-Research Center for Environment and Health, Neuherberg, Germany and supported by grants from the German Federal Ministry of Education and Research (BMBF), the German National Genome Research Network (NGFN) and the Munich Center of Health Sciences (MC Health) as part of LMUinnovativ. Additional funds were provided by the German Diabetes Center (Düsseldorf, Germany), the Federal Ministry of Health (Berlin, Germany) and the Ministry of Innovation, Science, Research and Technology of the state North Rhine-Westphalia (Düsseldorf, Germany). WR was supported by a research grant of the Deutsche Forschungsgemeinschaft (DFG, RA 459/2-1). We thank all members of field staffs who were involved in the planning and conduct of the MONICA/KORA Augsburg studies.

METSIM: Support was provided by grant 124243 from the Academy of Finland.

NHS/HPFS: Nurses Health Study/Health Professionals Follow-up Study-GENEVA studies are supported by NIH grants U01HG004399, DK58845, and CA87969.

Partners/Roche: We thank Roche Pharmaceuticals for its support and collaboration in assembling the Partners/Roche cohort. Supported by the Mallinckrodt General Clinical Research Program, National Center for Research Resources, NIH RR01066.

RISC: The RISC Study is supported by European Union grant QLG1-CT-2001-01252 and AstraZeneca. Laura Pascoe holds a BBSRC Case studentship with Unilever Ltd.

Rotterdam: The generation and management of GWAS genotype data for the Rotterdam Study is supported by the Netherlands Organization of Scientific Research NWO Investments (nr. 175.010.2005.011, 911-03-012), the Research Institute for Diseases in the Elderly (014-93-015; RIDE2),EUROSPAN (European Special Populations Research Network;LSHG-CT-2006-01947),the Netherlands Organization for Scientific Research (Pionier, 047.016.009, 047.017.043;050-060-810), Erasmus MC and the Centre for Medical Systems Biology (CMSB I and II and Grand; National Genomics Initiative) of the Netherlands Genomics Initiative (NGI); The Rotterdam Study is further funded by Erasmus Medical Center and Erasmus University, Rotterdam, Netherlands Organization for the Health Research and Development (ZonMw), the Research Institute for Diseases in the Elderly (RIDE), the Ministry of Education, Culture and Science, the Ministry for Health, Welfare and Sports, the European Commission (DG XII), and the Municipality of Rotterdam. We thank Pascal Arp, Mila Jhamai, Dr Michael Moorhouse, Marijn Verkerk, and Sander Bervoets for their help in creating the GWAS database. The authors are grateful to the study participants, the staff from the Rotterdam Study and the participating general practitioners and pharmacists.

Sorbs: Grants from the German Research Council (KFO-152 to Michael Stumvoll), from the IZKF (B27 to Michael Stumvoll, Peter Kovacs and Anke Tönjes) and from the German Diabetes Association (to Yvonne Böttcher, Peter Kovacs and Anke Tönjes)

Nature Genetics: doi:10.1038/ng.521

UKT2DGC: The Wellcome Trust (Functional Genomics Grant No: 072960) provides core support for Wellcome Trust United Kingdom Type 2 Diabetes Case Control Collection, based in Tayside Scotland. We are grateful to all participants who took part in this study, the general practitioners and Scottish School of Primary Care for their help in recruiting them, and the whole team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses. Ethical approval for the study was obtained from the Tissue Bank Committee and Tayside Committee on Medical Research Ethics.

ULSAM: Genotyping was performed by the SNP Technology Platform in Uppsala (www.genotyping.se). We thank Tomas Axelsson, Ann-Christine Wiman and Caisa Pöntinen for their excellent assistance with genotyping. The SNP Technology Platform is supported by Uppsala University and the Knut and Alice Wallenberg Foundation. E.I. is supported by grants from the Swedish Research Council and the Swedish Heart-Lung Foundation.

Whitehall II: The Whitehall II study has been supported by grants from the Medical Research Council; Economic and Social Research Council; British Heart Foundation; Health and Safety Executive; Department of Health; National Heart Lung and Blood Institute (HL36310), US, NIH: National Institute on Aging (AG13196), US, NIH; Agency for Health Care Policy Research (HS06516); and the John D and Catherine T MacArthur Foundation Research Networks on Successful Midlife Development and Socio-economic Status and Health. MM is supported by an MRC Research Professorship. Mika Kivimaki is supported by the Academy of Finland (grant 117604). Genotyping is supported by an MRC-GSK grant to the MRC Epidemiology Unit, Cambridge, UK.

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, G0601261): 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 and Jonathan Marchini (Oxford). The research was also supported by the Oxford NIHR Biomedical Research Centre.

Nature Genetics: doi:10.1038/ng.521

DISCLOSURES

J.B.M. currently has research grants from GlaxoSmithKline and Sanofi-aventis, and serves on consultancy boards for GlaxoSmithKline, Sanofi-aventis, Interleukin Genetics, Kalypsis, and Outcomes Sciences. J.C.F. has received consulting honoraria from Merck, bioStrategies, XOMA and Publicis Healthcare Communications Group, a global advertising agency engaged by Amylin Pharmaceuticals. deCODE authors are employees at deCODE genetics, and own stock or stock options in the company. P.W.F. has received consulting honoraria from Unilever. P.V. and G.W. received financial support from GlaxoSmithKline to build the CoLaus study. V.Mo., K.S. and D.M.W. are all full-time employees at GlaxoSmithKline. IB and spouse own stock in GlaxoSmithKline and Incyte. A.S. has research support from GlaxoSmithKline. R.M.W. has received consulting honoraria from Merck & Co. and Vivus Inc., currently has a grant from Merck & Co., and received research material support from Takeda Pharmaceuticals North America.

Nature Genetics: doi:10.1038/ng.521

GIANT CONSORTIUM MEMBERSHIP AND AFFILIATIONS

Cristen J Willer[1,77,78,] Elizabeth K Speliotes[2,3,77,78,] Ruth J F Loos[4,5,77,78,] Shengxu Li[4,5,77,78,] Cecilia M Lindgren[6,21,78], Iris M Heid[7,78], Sonja I Berndt[8], Amanda L Elliott[9,10], Anne U Jackson[1], Claudia Lamina[7], Guillaume Lettre[9,11], Noha Lim[12], Helen N Lyon[3,11], Steven A McCarroll[9,10], Konstantinos Papadakis[13], Lu Qi[14,15], Joshua C Randall[6], Rosa Maria Roccasecca[16], Serena Sanna[17], Paul Scheet[18], Michael N Weedon[19], Eleanor Wheeler[16], Jing Hua Zhao[4,5], Leonie C Jacobs[20], Inga Prokopenko[6,21], Nicole Soranzo[16,22], Toshiko Tanaka[23], Nicholas J Timpson[24], Peter Almgren[25], Amanda Bennett[21], Richard N Bergman[26], Sheila A Bingham[27,28], Lori L Bonnycastle[29], Morris Brown[30], Noël P Burtt[9], Peter Chines[29], Lachlan Coin[31], Francis S Collins[29], John M Connell[32], Cyrus Cooper[33], George Davey Smith[24], Elaine M Dennison[33], Parimal Deodhar[29], Paul Elliott[31], Michael R Erdos[29], Karol Estrada[20], David M Evans[24], Lauren Gianniny[9], Christian Gieger[7], Christopher J Gillson[4,5], Candace Guiducci[9], Rachel Hackett[9], David Hadley[13], Alistair S Hall[34], Aki S Havulinna[35], Johannes Hebebrand[36], Albert Hofman[37], Bo Isomaa[38], Kevin B Jacobs[39], Toby Johnson[40–42], Pekka Jousilahti[35], Zorica Jovanovic[5,43], Kay-Tee Khaw[44], Peter Kraft[45], Mikko Kuokkanen[9,46], Johanna Kuusisto[47], Jaana Laitinen[48], Edward G Lakatta[49], Jian'an Luan[4,5], Robert N Luben[44], Massimo Mangino[68], Wendy L McArdle[51], Thomas Meitinger[52,53], Antonella Mulas[17], Patricia B Munroe[54], Narisu Narisu[29], Andrew R Ness[55], Kate Northstone[51], Stephen O'Rahilly[5,43], Carolin Purmann[5,43], Matthew G Rees[29], Martin Ridderstråle[56], Susan M Ring[51], Fernando Rivadeneira[20,37], Aimo Ruokonen[57], Manjinder S Sandhu[4,44], Jouko Saramies[58], Laura J Scott[1], Angelo Scuteri[59], Kaisa Silander[46,70], Matthew A Sims[4,5], Kijoung Song[12], Jonathan Stephens[60], Suzanne Stevens[50], Heather M Stringham[1], Y C Loraine Tung[5,43], Timo T Valle[61], Cornelia M Van Duijn[37], Karani S Vimaleswaran[4,5], Peter Vollenweider[62], Gerard Waeber[62], Chris Wallace[54], Richard M Watanabe[63], Dawn M Waterworth[12], Nicholas Watkins[60], The Wellcome Trust Case Control Consortium[75], Jacqueline C M Witteman[37], Eleftheria Zeggini[16], Guangju Zhai[22], M Carola Zillikens[20], David Altshuler[9,10], Mark J Caulfield[54], Stephen J Chanock[8], I Sadaf Farooqi[5,43], Luigi Ferrucci[23], Jack M Guralnik[64], Andrew T Hattersley[65], Frank B Hu[14,15], Marjo-Riitta Jarvelin[31], Markku Laakso[47], Vincent Mooser[12], Ken K Ong[4,5], Willem H Ouwehand[16,60], Veikko Salomaa[35], Nilesh J Samani[50], Timothy D Spector[22], Tiinamaija Tuomi[66,67], Jaakko Tuomilehto[66], Manuela Uda[17], André G Uitterlinden[20,37], Nicholas J Wareham[4,5], Panagiotis Deloukas[16], Timothy M Frayling[19], Leif C Groop[25], Richard B Hayes[8], David J Hunter[9,14,15,45,] Karen L Mohlke[69], Leena Peltonen[9,16,70], David Schlessinger[71], David P Strachan[13], H-Erich Wichmann[7,72,73], Mark I McCarthy[6,21,74,78,79,] Michael Boehnke[1,78,79], Inês Barroso[16,78,79], Gonçalo R Abecasis[18,78,79] & Joel N Hirschhorn[3,11,74,78,79] for the GIANT Consortium[80]

1. Center for Statistical Genetics, Department of Biostatistics, University of Michigan School of Public Health, Ann Arbor, Michigan 48109, USA.

2. Division of Gastroenterology, Massachusetts General Hospital, Boston, Massachusetts 02114, USA.

3. Metabolism Initiative and Program in Medical and Population Genetics, Broad Institute of Harvard and Massachusetts Institute of Technology, Boston, Massachusetts 02142, USA.

Nature Genetics: doi:10.1038/ng.521

4. Medical Research Council Epidemiology Unit, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK.
5. Institute of Metabolic Science, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK.
6. Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford OX3 7BN, UK.
7. Institute of Epidemiology, Helmholtz Zentrum München, Ingolstaedter Landstrasse 1, 85764 Neuherberg, Germany.
8. Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland 20892, USA.
9. Program in Medical and Population Genetics, BroadInstitute of MIT and Harvard, Cambridge, Massachusetts 02142, USA.
10. Center for Human Genetic Research, Massachusetts General Hospital, Boston, Massachusetts 02114, USA.
11. Program in Genomics and Divisions of Endocrinology and Genetics, Children's Hospital, Boston, Massachusetts 02115, USA.
12. Medical Genetics/Clinical Pharmacology and Discovery Medicine, Glaxo SmithKline, King of Prussia, Pennsylvania 19406, USA.
13. Division of Community Health Sciences, St. George's, University of London, London SW17 0RE, UK.
14. Department of Nutrition, Harvard School of Public Health, Boston, Massachusetts 02115, USA.
15. Channing Laboratory, Department of Medicine,
Brigham and Women's Hospital, Boston, Massachusetts 02115, USA.
16. Wellcome Trust Sanger Institute, Hinxton, Cambridge CB10 1SA, UK.
17. Istituto di Neurogenetica e Neurofarmacologia, Consiglio Nazionale delle Ricerche, Cagliari 09042, Italy.
18. Department of Epidemiology, University of Texas, M.D. Anderson Cancer Center, Houston, Texas, 77030, USA.
19. Genetics of Complex Traits, Peninsula Medical School, Exeter EX1 2LU, UK.
20. Department of Internal Medicine, Erasmus MC, PO Box 2400, NL-3000-CA Rotterdam, Netherlands.
21. Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Churchill Hospital, Oxford OX3 7LJ, UK.
22. Department of Twin Research and Genetic Epidemiology, King's College London, London SE1 7EH, UK.
23. Clinical Research Branch, National Institute on Aging, Baltimore, Maryland 21250, USA.
24. MRC Centre for Causal Analyses in Translational Epidemiology, Department of Social Medicine, University of Bristol, Bristol BS8 2PR, UK.
25. Lund University Diabetes Centre, Department of Clinical Sciences, Lund University, 20502 Malmö, Sweden.
26. Physiology and Biophysics, University of Southern California School of Medicine, Los Angeles, California 90033, USA.
27. MRC Dunn Human Nutrition Unit, Wellcome Trust/MRC Building, Cambridge CB2 0XY, UK.
28. MRC Centre for Nutritional Epidemiology in Cancer Prevention and Survival,
Cambridge CB1 8RN, UK.
29. National Human Genome Research Institute, Bethesda, Maryland 20892, USA.
30. Clinical Pharmacology Unit, University of Cambridge, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK.

Nature Genetics: doi:10.1038/ng.521

31. Department of Epidemiology and Public Health, Imperial College London, St. Mary's Campus, Norfolk Place, London W21PG, UK.
32. British Heart Foundation Glasgow Cardiovascular Research Centre, Faculty of Medicine, University of Glasgow, Glasgow G12 8TA, UK.
33. MRC Epidemiology Resource Centre, University of Southampton, Southampton General Hospital, Southampton SO16 6YD, UK.
34. Yorkshire Heart Centre, Leeds General Infirmary, Leeds LS13EX, UK.
35. National Institute for Health and Welfare, Unit of Chronic Disease Epidemiology and Prevention, Helsinki, Finland.
36. Department of Child and Adolescent Psychiatry, University of Duisburg-Essen, Virchowstr. 174, 45147 Essen, Germany.
37. Department of Epidemiology, Erasmus MC, PO Box 2400, NL-3000-CA Rotterdam, The Netherlands.
38. Folkhalsan Research Center, Malmska Municipal Health Care Center and Hospital, FIN-00014 Jakobstad, Finland.
39. Bioinformed Consulting Services, Gaithersburg, Maryland 20877, USA.
40. Department of Medical Genetics, University of Lausanne, CH-1005 Lausanne, Switzerland.
41. University Institute for Social and Preventative Medicine, Centre Hospitalier Universitaire Vaudois (CHUV), CH-1005 Lausanne, Switzerland.
42. Swiss Institute of Bioinformatics, CH-1005 Lausanne, Switzerland.
43. University of Cambridge Metabolic Research Laboratories, Addenbrooke's Hospital, Cambridge CB2 0QQ, UK.
44. Department of Public Health and Primary Care, Institute of Public Health, University of Cambridge, Cambridge CB2 0SR, UK.
45. Program in Molecular and Genetic Epidemiology, Harvard School of Public Health, Boston, Massachusetts 02115, USA.
46. National Institute for Health and Welfare, Unit of Public Health Genomics, Helsinki, Finland.
47. Department of Medicine, University of Kuopio, 70210 Kuopio, Finland.
48. Finnish Institute of Occupational Health, Aapistie 1, Fin-90220 Oulu, Finland.
49. Laboratory of Cardiovascular Science, Gerontology Research Center, National Institute on Aging, Baltimore, Maryland 21224, USA.
50. Department of Cardiovascular Sciences, University of Leicester, Clinical Sciences, Glenfield General Hospital, Leicester LE3 9QP, UK.
51. Avon Longitudinal Study of Parents and Children (ALSPAC), Department of Social Medicine, University of Bristol, Bristol BS8 1TQ, UK.
52. Institute of Human Genetics, Helmholtz Zentrum München, Ingolstaedter Landstrasse 1, 85764 Neuherberg, Germany.
53. Institute of Human Genetics, Technical University Munich, D-81765, Munich, Germany.
54. Clinical Pharmacology, The William Harvey Research Institute, Bart's and The London, Queen Mary's School of Medicine and Dentistry, Charterhouse Square, London EC1M 6BQ, UK.
55. Department of Oral & Dental Science, University of Bristol, Bristol BS1 2LY, UK.
56. Department of Clinical Sciences, Lund University, 20502 Malmö, Sweden.
57. Department of Clinical Chemistry, University of Oulu, Fin-90220 Oulu, Finland.
58. Savitaipale Health Center, FIN-54800 Savitaipale, Finland.
59. UO Geriatria - Istituto Nazionale Ricovero e Cura per Anziani (INRCA IRCCS) - Rome, Italy.
60. Department of Haematology, University of Cambridge/NHS Blood & Transplant, Cambridge CB2 2PR, UK.
61. National Institute for Health and Welfare, Unit of Diabetes Prevention, Helsinki, Finland.

Nature Genetics: doi:10.1038/ng.521

62. Department of Internal Medicine, BH-10 Centre Hospitalier Universitaire Vaudois (CHUV), 1011 Lausanne, Switzerland.
63. Department of Preventive Medicine, Division of Biostatistics, Keck School of Medicine, University of Southern California, CHP-220, Los Angeles, California 90089, USA.
64. Laboratory of Epidemiology, Demography, and Biometry; Gerontology Research Center, National Institute on Aging, Bethesda, Maryland 20892, USA.
65. Peninsula Medical School, Exeter EX5 2DW, UK.
66. Department of Public Health, University of Helsinki, Helsinki, Finland.
67. Department of Medicine, Helsinki University Hospital, Helsinki, Finland and Folkhalsan Research Centre, Helsinki, Finland.
68. Twin Research & Genetic Epidemiology Department, King's College London, St Thomas' Hospital Campus, Lambeth Palace Rd, London SE1 7EH, UK.
69. Department of Genetics, University of North Carolina, CB #7264, Chapel Hill, North Carolina 27599, USA.
70. Institute for Molecular Medicine Finland FIMM, University of Helsinki, Helsinki, Finland.
71. Genome Technology Branch, National Human Genome Research Institute, Bethesda, Maryland 20892, USA.
72. Institute of Medical Information Processing, Biometry, and Epidemiology, Ludwig-Maximilians-University München, Marchioninistrasse 15, 81377 München, Germany.
73. Klinikum Grosshadern, Munich, Germany
74. National Institute for Health Research, Oxford Biomedical Research Centre, University of Oxford, Old Road, Headington, Oxford OX3 7LJ, UK.
75. Department of Genetics, Harvard Medical School, Boston, Massachusetts 02115, USA.
76. A full list of members is provided in the Supplementary Note of Willer Nature Genetics 40:161-169 (2008).
77. These authors contributed equally to this work.
78. Members of the writing team.
79. These authors jointly directed the project.
80. All authors are members of the Genetic Investigation of ANthropometric Traits (GIANT) Consortium.

Nature Genetics: doi:10.1038/ng.521

REFERENCES

1. Lukowiak, B. et al. Identification and purification of functional human beta-cells by a new specific zinc-fluorescent probe. *J Histochem Cytochem* **49**, 519-28 (2001).
2. Psaty, B.M. et al. Design of prospective meta-analyses of genome-wide association studies from five cohorts. *Circulation Genetics* **in press**(2009).
3. Sladek, R. et al. A genome-wide association study identifies novel risk loci for type 2 diabetes. *Nature* **445**, 881-5 (2007).
4. Steinthorsdottir, V. et al. A variant in CDKAL1 influences insulin response and risk of type 2 diabetes. *Nat Genet* **39**, 770-5 (2007).
5. Thorleifsson, G. et al. Genome-wide association yields new sequence variants at seven loci that associate with measures of obesity. *Nat Genet* **41**, 18-24 (2009).
6. Saxena, R. et al. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. *Science* **316**, 1331-6 (2007).
7. Zeggini, E. et al. Meta-analysis of genome-wide association data and large-scale replication identifies additional susceptibility loci for type 2 diabetes. *Nat Genet* **40**, 638-45 (2008).
8. Jorgensen, T. et al. A randomized non-pharmacological intervention study for prevention of ischaemic heart disease: baseline results Inter99. *Eur J Cardiovasc Prev Rehabil* **10**, 377-86 (2003).
9. Lauritzen, T. et al. The ADDITION study: proposed trial of the cost-effectiveness of an intensive multifactorial intervention on morbidity and mortality among people with Type 2 diabetes detected by screening. *Int J Obes Relat Metab Disord* **24 Suppl 3**, S6-11 (2000).
10. Sparso, T. et al. The GCKR rs780094 polymorphism is associated with elevated fasting serum triacylglycerol, reduced fasting and OGTT-related insulinaemia, and reduced risk of type 2 diabetes. *Diabetologia* **51**, 70-5 (2008).
11. Schwarz, P.E. et al. Hypoadiponectinemia is associated with progression toward type 2 diabetes and genetic variation in the ADIPOQ gene promoter. *Diabetes Care* **29**, 1645-50 (2006).
12. Bouatia-Naji, N. et al. A variant near MTNR1B is associated with increased fasting plasma glucose levels and type 2 diabetes risk. *Nat Genet* **41**, 89-94 (2009).
13. Scott, L.J. et al. A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. *Science* **316**, 1341-5 (2007).
14. Halsall, D.J., McFarlane, I., Luan, J., Cox, T.M. & Wareham, N.J. Typical type 2 diabetes mellitus and HFE gene mutations: a population-based case - control study. *Hum Mol Genet* **12**, 1361-5 (2003).
15. Loos, R.J. et al. TCF7L2 polymorphisms modulate proinsulin levels and beta-cell function in a British Europid population. *Diabetes* **56**, 1943-7 (2007).
16. Rimm, E.B. et al. Prospective study of alcohol consumption and risk of coronary disease in men. *Lancet* **338**, 464-8 (1991).

Nature Genetics: doi:10.1038/ng.521

17. Cornelis, M.C. et al. Joint effects of common genetic variants on the risk for type 2 diabetes in U.S. men and women of European ancestry. *Ann Intern Med* **150**, 541-50 (2009).
18. Herder, C. et al. Variants of the PPARG, IGF2BP2, CDKAL1, HHEX, and TCF7L2 genes confer risk of type 2 diabetes independently of BMI in the German KORA studies. *Horm Metab Res* **40**, 722-6 (2008).
19. Wichmann, H.E., Gieger, C. & Illig, T. KORA-gen--resource for population genetics, controls and a broad spectrum of disease phenotypes. *Gesundheitswesen* **67 Suppl 1**, S26-30 (2005).
20. Berglund, G. et al. Long-term outcome of the Malmo preventive project: mortality and cardiovascular morbidity. *J Intern Med* **247**, 19-29 (2000).
21. Lyssenko, V. et al. Clinical risk factors, DNA variants, and the development of type 2 diabetes. *N Engl J Med* **359**, 2220-32 (2008).
22. Stancakova, A. et al. Changes in insulin sensitivity and insulin release in relation to glycemia and glucose tolerance in 6,414 Finnish men. *Diabetes* **58**, 1212-21 (2009).
23. Colditz, G.A. & Hankinson, S.E. The Nurses' Health Study: lifestyle and health among women. *Nat Rev Cancer* **5**, 388-96 (2005).
24. Ai, M. et al. Glycated albumin and direct low density lipoprotein cholesterol levels in type 2diabetes mellitus. *Clinica Chimica Acta* **In press**(2009).
25. Prokopenko, I. et al. Variants in MTNR1B influence fasting glucose levels. *Nat Genet* **41**, 77-81 (2009).
26. Zeggini, E. et al. Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. *Science* **316**, 1336-41 (2007).

Nature Genetics: doi:10.1038/ng.521

Supplementary Table 1. Cohort and study characteristics and details of analysis metrics and methods

	discovery cohorts									replication cohorts															
STUDY SAMPLE	**ARIC**	**BLSA**	**CHS-stage 1&2**	**CoLaus**	**DGI**	**Fenland**	**Framingham Offspring Cohort**	**FUSION**	**Sorbs**	**Amish (AFDS)**	**BotniaPPP**	**CHS-stage 3**	**DIAGEN**	**ELY**	**French Obese Adults**	**FUSIONs2**	**Haguenau cohort**	**Hertfordshire**	**Inter99**	**METSIM**	**NHANES**	**Obesity family relatives**	**RISC**	**Roche**	**ULSAM**	**WhiteHall II**
Source Country	USA	USA	USA	Switzerland	Finland, Sweden	UK	USA	Finland	Germany	United States	Finland	USA	Germany	UK	France	Finland	France	UK	Denmark	Finland	USA	France	Multi-centre	USA	Sweden	UK
Study Type	Population-based	Population-based	Population-based	Population-based	Case-control	Population-based	Population-based	Case-control	Population-based	Population-based	Population-based	Population-based	Population-based	Population-based	Case-control	Case-control	Case-control for smallness for gestational age	Population-based	Population-based	Population-based	Population-based	Obesity Families	Population-based	Case-Control	Population-based	Population-based
GLUCOSE MEASUREMENTS																										
Sample	EDTA plasma and OGTT	Fasting plasma and OGTT	12-hr fasting serum and OGTT	Fasting venous fresh and OGTT (120 mins) frozen plasma	Fasting and OGTT plasma and blood	Fasting and OGTT (120 min) venous fresh plasma with fluoride	Fasting and OGTT plasma	Fasting and OGTT plasma	75g OGTT (fasting, 30 min, 120 min), serum	Fasting and OGTT plasma	Fasting and OGTT plasma	12-hr fasting serum and OGTT	Fasting and OGTT plasma	Fasting fresh venous plasma, OGTT (30, 60, 120 mins)	Fasting plasma, 5 points 2H OGTT	Fasting and OGTT plasma and whole blood (converted)	Fasting plasma, 3 points 2H OGTT[15]	Fasting and OGTT (30, 120 mins) venous plasma	Fasting plasma, 3 points (0 min, 30 min, 120 min) 2H OGTT	Fasting and OGTT plasma	Fasting and OGTT plasma	Fasting plasma, 5 points 2H OGTT	Fasting and OGTT (30, 60, 90 120 mins) fresh venous plasma in lithium heparin or sodium fluoride with heparin [16]	Fasting and OGTT plasma	Fasting and OGTTplasma [17]	Fasting plasma, OGTT (120 mins)
Collection method	Red cells removed within 30 minutes, samples frozen and shipped to central lab	Overnight fast	venipuncture was performed on study participants under 12-hour fasting conditions	Fasting: centrifuged and analyzed within 2 hours; 120 mins: blood was immediatelly centrifuged and plasma frozen at -80C until measurement	12 hour overnight fast	Plasma centrifuged immediately and analyzed same day (within 4h)	≥8 hr overnight fast	Overnight fast and plasma collected in EDTA tubes	overnight fasting, spinning within 1 hour after collection, then immediate quick-freeze on dry ice before transport, further storage in -80°C freezer	Venous (grey top - NaF)	12 hour overnight fast	venipuncture was performed on study participants under 12-hour fasting conditions	10 hour minimum overnight fast	Centrifuged and analyzed immediately	Morning after overnight fast		Morning after overnight fast	Venous blood was centrifuged and plasma frozen at -80C until transported to lab for measurement	Venous after 10 hrs fast		Venous	Morning after overnight fast	Tubes placed immediately onto ice and centrifuged within 15 mins at 4oC	Venous, ≥8 hr overnight fast	Venous	Venous
Assay	Hexokinase assay [4]	ELISA (Alpco Diagnostic) [3]	Kodak Ektachem 700 Analyzer [6,7]	Fasting: glucose dehydrogenase (Roche Diagnostics, CH); 120 mins: glucose oxidase methode (Beckmann, Fullerton)	Glucose oxidase method (Beckman Glucose Analyzer, Beckman Instruments, Fullerton, CA) [10]	Fasting and 120 min: Hexokinase/ glucose-6-phosphate dehydrogenase (Dimension RxL, Siemens)	Hexokinase reagent kit (a-gent glucose test, Abbott, South Pasadena, California)	Glucose oxidase method (Yellow Springs instruments, Yellow Springs, OH and autoanalyser) and hexokinase method	hexokinase method (Automated analyser Modular, Roche Diagnostics, Mannheim, Germany).	Glucose oxidase (Beckman, Fullerton, CA)	Glucose dehydrogenase method (Hemocue, Angelholm, Sweden) [14]	Kodak Ektachem 700 Analyzer [18,19]		Hexokinase assay	Glucose oxidase colorimetric assay		Glucose oxidase colorimetric assay	Glucose oxidase method (Advia 1650 autoanalyser, Bayer Diagnostics UK)	hexokinase/G6P-DH technique (Boehringer Mannheim, Germany).	enzymatic hexokinase phtometric assay (Konelab System Reagents, Thermo Fischer Scientific, Vaasa, Finland)	Hexokinase	Glucose oxidase colorimetric assay	Glucose oxidase method (Cobas Integra, Roche)	Hexokinase	Glucose dehydrogenase method (Gluc-DH, Merck, Darmstadt, Germany)	Electrochemical glucose oxidase
INSULIN MEASUREMENTS																										
Sample (Fasting? Blood? Serum?)	n.a.	Fasting plasma	Fasting serum	Fasting frozen venous plasma; 120 mins insulin not available	serum insulin	n.a.	Fasting plasma insulin and 2h OGTT	fasting plasma (FUSION) and serum (Finrisk02)	75g OGTT (fasting, 30 min, 120 min), serum	Fasting plasma	serum insulin	Fasting serum	Fasting plasma insulin	Fasting frozen venous plasma, OGTT (30, 60, 120 mins) frozen venous plasma	Fasting plasma, 5 points OGTT including 2h	Fasting and OGTT serum or plasma	Fasting plasma, 3 points OGTT, including 2h	Fasting and OGTT (30, 120 mins) venous plasma	Fasting and OGTT serum	Fasting and OGTT serum	Fasting and OGTT plasma	Fasting plasma, 5 points OGTT, including 2h	Fasting and OGTT (30, 60, 90 120 mins) fresh venous serum	fasting, 3 points OGTT, 2h levels	Fasting and OGTT plasma	Fasting serum, OGTT (120 mins)
STUDY SAMPLE	**ARIC**	**BLSA**	**CHS-stage 1&2**	**CoLaus**	**DGI**	**Fenland**	**Framingham Offspring Cohort**	**FUSION**	**Sorbs**	**Amish (AFDS)**	**BotniaPPP**	**CHS-stage 3**	**DIAGEN**	**ELY**	**French Obese Adults**	**FUSIONs2**	**Haguenau cohort**	**Hertfordshire**	**Inter99**	**METSIM**	**NHANES**	**Obesity family relatives**	**RISC**	**Roche**	**ULSAM**	**WhiteHall II**
Assay	n.a.	glucose analyzer (Beckman Instruments) [3]	Kodak Ektachem 700 Analyzer [8]	Solid-phase, two-site chemiluminescent immunometric assay [8]	radioimmunoassay (Pharmacia, Uppsala, Sweden), enzyme linked immunoassay (DAKO Diagnostics Ltd, Cambridgeshire, UK), fluoroimmunometric assay (AutoDelfia, Perkin Elmer Finland, Turku, Finland) [10]	n.a.	DPC Coat-A-Count RIA (total immunoreactive insulin)	RIA with dextran charcoal separation [11]	AutoDELFIA Insulin assay (PerkinElmer Life and Analytical Sciences, Turku, Finland) [13]	RIA (Linco, St. Louis, MO)	Fluoroimmunometric assay (Delfia, Perkin Elmer Finland, Turku, Finland) [14]	Kodak Ektachem 700 Analyzer		Immunometric assay	Double anti-body radioimmuno-assay		Double anti-body radioimmuno-assay [15]	Immunofluorimetric two-site assays (DELFIA system)	ELISA (AutoDELFIA, Perkin Elmer-Wallac) [20]	immunoassay (ADVIA Centaur Insulin RIA, no. 02230141, Siemens Medical Solutions Diagnostics, Tarrytown, NY)	Pharmacia Insulin RIA (Pharmacia Diagnostics AB, Uppsala, Sweden	Double anti-body radioimmuno-assay	Specific time-resolved fluroimmunoassay (AutoDELFIA Insulin kit; Wallac Oy, Turku, Finland) [16]	Human specific insulin RIA, Linco Research Inc., St Louis MO, USA.	Immunoreactive insulin: Enzymatic-immunological assay (Enzymun, Boehringer Mannheim) [17]	Double antibody ELISA
Assay sensitivity	n.a.	n.a.	n.a.	Maximum intra-assay CV of 13.7%.	n.a.	n.a.	1.2 microU/mL	CV=11% low conc, 13% high conc	3.0 pmol/L	2-200 mU/L		n.a.		Maximum intra-assay CV of 6.6%				Inter-assay CV of 6 to 10%	3 pmol/l, CV<6%		2.5 µIU/mL			2µU/ml		Maximum inter- and intra-assay CV less than 8%
SAMPLES																										
EXCLUSIONS	Ineligible for OGTT (currently treated with anti-diabetes medications, fasting < 10 hours, prior surgery to remove stomach or small intestine, on dialysis; 638) eligible but refused OGTT (412); technical problem with OGTT (106); prevalent diabetes based on fasting glucose > 7 mmol/L or self-reported physician diagnosis / 329	Diabetes/non-European descent	Prevalent coronary heart disease (n=1195), congestive heart failure (n=86), peripheral vascular disease (n=93), valvular heart disease (n=20), stroke (n=166) or transient ischemic attack (n=56), persons with multiple events are listed by initial exclusionary event. Use of diabetes meds or fasting glucose >= 7mmols.	Known T2D, glucose >= 7mmols	Diabetes ascertained by OGTT, medical record review or GAD Ab positivity	Known T2D, fasting glucose >= 7mmols	Non-fasting individuals, Type 1 diabetes, Other diabetic treatment, Fasting glucose ≥ 7 mmol/L	Diabetes ascertained by OGTT, medical record review or GAD Ab positivity; diabetes medication, missing 2-hr glucose values	non-fasting individuals, known type 1 or type 2 diabetes, diabetes ascertained by OGTT		T2D	see CHS-stage 1&2 exclusions	Known diabetic, fg>=7mmol/l	Diabetes, FG>=7 mmol/L	Known T2D or Fasting glucose > 7mmol/l	T2D	Known T2D or Fasting glucose > 7mmol/l	Diabetes, FG>=7 mmol/L	T2D	Known diabetic, on diabetes medication	T2D	Known T2D or Fasting glucose > 7mmol/l	Diabetes, FG>=7 mmol/L	T2D	T2D	Diabetes, FG>=7 mmol/L
STUDY SAMPLE	**ARIC**	**BLSA**	**CHS-stage 1&2**	**CoLaus**	**DGI**	**Fenland**	**Framingham Offspring Cohort**	**FUSION**	**Sorbs**	**Amish (AFDS)**	**BotniaPPP**	**CHS-stage 3**	**DIAGEN**	**ELY**	**French Obese Adults**	**FUSIONs2**	**Haguenau cohort**	**Hertfordshire**	**Inter99**	**METSIM**	**NHANES**	**Obesity family relatives**	**RISC**	**Roche**	**ULSAM**	**WhiteHall II**
Samples with 2hr GLUCOSE phenotype (uniform analysis): N all (%males/%females)	5,083 (45.0/ 55.0)	475 (52.8/47.2)	1,676 (43, 57)	541 (39.7/60.3)	1,432 (48.4/51.6)	1,371 (44/56)	2,722 (45, 55)	1,233 (50.0/50.0)	823 (41/59)	778 (47.0/53.0)	2,869 (45.6/54.4)	n.a.	1,171 (42.2/57.8)	1,497 (45.6/54.4)	304 (19.7/80.3)	1,000 (57.8/42.2)	1,370 (47.7/52.3)	1,878 (54.3/ 45.7)	5,778 (49.1/50.9)	5,978 (100/0)	531 (39.7 / 60.3)	314 (47.1/52.9)	1,461 (44.7/55.3)	605 (46.61/53.39)	949 (100/0)	4,346 (73.9/26.1)
Age [Mean (sd) males / Mean (sd) females], years	63.3 (5.7) / 62.6 (5.5)	71.9 (13.3) / 67.2 (15.2)	73.4 (5.7) / 73.0 (5.4)	52.26 (10.74) / 53.73 (10.73)	58.7 (10.4) / 59.4 (10.2)	44.42 (7.35) / 45.41 (7.21)	54.01 (9.84) / 54.04 (9.76)	60.4(11.5) / 61.5 (10.8)	46.14(16.30)/ 46.45(15.69)	45.1 (14.9) / 43.7 (14.5)	47.0 (16.2) / 47.2 (16.1)	n.a.	60.3 (14.5) / 60.2 (15.4)	61.2 (9.2) / 60.6 (9.1)	45.0 (11.7) / 44.0 (12.1)	57.4 (7.6) / 60.9 (7.4)	22.1 (3.9) / 22.1 (4.0)	65.9 (2.9) / 66.6 (2.7)	46.2 (7.8) / 45.7 (7.9)]	57.4 (6.8) /	57.3 (10.6) / 56.8 (10.6)	39.0 (8.9) / 37.1 (7.9)	43.4 (8.5) / 44.6 (8.2)	52.6 (12.6) / 53.3 (12.5)	71.0 (0.6) /	60.6 (5.9) / 61.0 (6.0)
BMI [Mean (sd) males / Mean (sd) females], kg/m2	28.2 (4.2) / 27.8 (5.6)	26.9 (3.9) / 25.4 (4.5)	26.1 (3.4) / 26.1 (3.4)	26.26 (3.77) / 24.87 (4.59)	26.6 (3.2) / 26.7(4.2)	27.56 (3.90) / 26.61 (5.36)	27.78 (3.84) / 26.14 (5.01)	27.0 (3.5) / 27.1 (4.3)	26.63(4.12)/ 26.48(5.69)	26.2 (3.9) / 27.7 (5.4)	26.4 (3.7) / 25.7 (4.7)	n.a.	27.0 (3.5) / 27.0 (5.1)	27.1 (3.9) / 27.1 (5.4)	48.2 (8.6) / 47.0 (7.3)	26.7 (3.4) / 27.1 (4.6)	23.0 (3.9) / 22.2 (4.3)	26.7 (3.4) / 27.1 (4.6)	26.6 (3.8) / 25.5 (4.8)	26.8 (3.8) /	27.7 (4.4) / 27.4 (5.9)	28.3 (6.0) / 30.7 (7.8)	26.5 (3.5) / 24.9 (4.4)	27.8 (5.2) / 27.2 (7.4)	26.0 (3.2) /	26.4 (3.7) / 26.6 (5.2)
2 hour glucose [Mean (sd) males / Mean (sd) females], mmol/l	6.97 (2.23) / 7.49 (2.33)	6.94 (2.44)/6.41 (2.02)	7.5 (2.4) / 7.9 (2.5)	6.25 (3.01) /5.73 (2.36)	5.46(1.30) /5.75(1.26)	5.29(1.45) / 5.20 (1.48)	5.72 (1.59) / 5.96 (1.66)	5.56(1.21) / 5.67(1.14)	5.36(2.52)/ 5.80(2.20)	5.7 (1.7) / 6.6 (1.7)	5.1 (1.7) / 5.3 (1.5)	n.a.	6.6 (1.9) / 6.6 (1.7)	6.1 (1.9) / 6.0 (1.8)	7.0 (2.3) / 6.4 (1.7)	5.4 (1.2) / 5.7 (1.1)	5.3 (1.2) / 5.4 (1.2)	6.9 (2.1) / 7.4 (2.1)	5.9 (1.6) / 6.0 (1.5)	6.1 (1.7) /	6.3 (1.7) / 6.5 (1.8)	4.9 (1.3) / 5.2 (1.2)	5.8 (1.7) / 5.8 (1.6)	5.7 (1.9) / 5.8 (1.8)	7.2 (2.3) /	6.4 (1.8)/ 6.4 (1.8)
Fasting PLASMA glucose [Mean (sd) males / Mean (sd) females], mmol/l	5.62 (0.49) /5.38 (0.50)	5.24 (0.55) / 4.93 (0.45)	5.7 (0.5) / 5.5 (0.6)	5.79 (1.54)/ 5.31 (0.79)	5.28 (0.49)/ 5.25 (0.46)	5.01 (0.47) / 4.74 (0.48)	5.35 (0.45) / 5.06 (0.47)	5.44 (0.45) / 5.19 (0.47)	5.55(0.92)/ 5.24(0.67)	5.09 (0.47) / 4.97 (0.46)	5.19 (0.57) / 5.14 (0.54)	n.a.	5.69 (0.63) / 5.46 (0.65)	5.10 (0.53) / 4.88 (0.53)	5.70 (0.65) / 5.50 (0.62)	5.28 (0.48) / 5.22 (0.44)	4.93 (0.35) / 4.66 (0.35)	5.87 (0.50) / 5.70 (0.50)	5.61 (0.49) / 5.30 (0.49)]	5.69 (0.49) /	5.46 (0.47) / 5.24 (0.52)	5.27 (0.43) / 4.95 (0.50)	5.24 (0.52) / 4.95 (0.58)	4.97 (0.47) / 4.78 (0.49)	5.4 (0.6) /	5.32 (0.50) / 5.09 (0.49)

Supplementary Table 1. Cohort and study characteristics and details of analysis metrics and methods

	discovery cohorts									replication cohorts															
STUDY SAMPLE	**ARIC**	**BLSA**	**CHS-stage 1&2**	**CoLaus**	**DGI**	**Fenland**	**Framingham Offspring Cohort**	**FUSION**	**Sorbs**	**Amish (AFDS)**	**BotniaPPP**	**CHS-stage 3**	**DIAGEN**	**ELY**	**French Obese Adults**	**FUSIONs2**	**Haguenau cohort**	**Hertfordshire**	**Inter99**	**METSIM**	**NHANES**	**Obesity family relatives**	**RISC**	**Roche**	**ULSAM**	**WhiteHall II**
Fasting PLASMA insulin(Mean (sd) males / Mean (sd) females), pmol/l	n.a.	48.6 (34.0) / 39.5 (22.2)	94.0 (45.8) / 93.7 (49.9)	64.2 (39.0)/ 52.2 (30.0)	42.17(35.78) /40.1(24.53)	n.a.	181.44 (67.44) / 163.17 (52.07)	54.9(32.4)/58.6(37 .3)	38.07(24.59)/ 40.82(25.68)	78.0 (52.1) /76.7 (33.2)	40.5 (31.4) / 38.3 (35.6)	n.a.	85.4 (47.0) / 78.1 (42.7)	58.8 (35.0) / 54.2 (34.8)	120.0 (71.4) / 88.5 (62.8)	48.4 (29.9) / 47.7 (26.2)	33.8 (21.9) / 37.6 (22.3)	87.6 (68.6) / 83.7 (57.4)	41.0 (26.0) / 40.3 (26.1)	48.7 (33.3)/	64.9 (34.6) / 59.2 (35.9)	38.2 (29.6) / 39.8 (30.0)	38.2 (20.8) / 34.2 (19.4)	89.0 (63.1) / 82.2 (79.7)	73.3 (39.8) /	52.0 (36.2)/ 46.4 (34.3)
Samples with 2hr insulin phenotype (uniform analysis): N all (%males/%females)	n.a.	468 (53.2/46.8)	1,676 (43, 57)	n.a.	1,120 (47.8/52.1)	n.a.	2,650 (46/ 54)	581 (41.0/59.0)	833(41.1/58.9)	764 (47.3/52.7)	2,775 (45.9/54.1)	n.a.	1,023 (41.7/58.3	1485 (45.4/55.6)	281 (18.9/81.1)	290 (53.8/46.2)	1,312 (47.5/52.5	n.a.	5,588 (49.1/50.9	5,971 (100/0)	529 (39.7 / 60.3)	282 (45.4/54.6)	1,324 (44.8/55.2)	605 (46.6/53.4)	942 (100/0)	4,346 (73.9/26.1)
2 hour insulin [Mean (sd) males / Mean (sd) females), pmol/l	n.a.	330.0 (322.1) / 281.5 (259.0)	523.8 (394.8) / 598.0 (459.5)	n.a.	208.0(190.7) /240.3 (171.4)	n.a.	553.9 (427.7) / 551.66 (356.5)	344.4(248.7) /387.7(277.3)	149.5(172.6)/ 200.3(159.8)	185.0 (160.77) / 318.38 (262.81)	182.6 (196.1) / 217.6 (226.7)	n.a.	420.5 (1066.2) / 366.8 (318.1)	353.5 (334.2) / 329.2 (312.0)	511.2 (504.1) / 341.8 (295.9)	215.8 (200.5) / 248.4 (163.8)	162.8 (142.2) / 254.1 (225.3)	n.a.	207 (192) / 207 (207)]	307.6 (308.8) /	312.9 (244.1) / 329.5 (274.9)	124.4 (134.3) / 168.7 (150.2)	204.1 (222.0) / 217.8 (222.6)	331.1 (285.5) / 360.9 (382.0)	422.6 (314.9) /	307.4 (272.4) / 307.6 (261.2)
GENOTYPING																										
Genotyping platform & SNP panel	Affymetrix SNP Array 6.0	Illumina550K	Illumina 370CNV duo	Affymetrix 500K Array Set	Affymetrix 500K Array Set	Affymetrix 500K Array Set	Affymetrix 500K and MIPS 50K	Illumina HumanHap300 and 1536 T2D candidate gene SNPs	Affymetrix 500K Array Set and Affymetrix SNP Array 6.0	Affymetrix 100K Chip (Santa Clara, CA); Taqman (Applied Biosystems, Foster City, CA)	iPLEX Sequenom MassARRAY	Illumina 370CNV duo	iPLEX Sequenom MassARRAY	n.a.	Illumina Human CNV370-Duo Array	iPLEX Sequenom MassARRAY	TaqMan assays	n.a.	TagMan	iPLEX Sequenom MassARRAY	iPLEX Sequenom MassARRAY	TaqMan assays	n.a.	iPLEX Sequenom MassARRAY	SNPstream system (Beckman Coulter)	n.a.
Genotyping centre	Broad Institute, Cambridge, MA, USA	NIA, USA	General Clinical Research Center's Phenotyping/Genotyping Laboratory at Cedars-Sinai, USA	Affymetrix Santa Clara, CA, USA	Broad Institute, Cambridge, MA, USA	Affymetrix Santa Clara, CA, USA	Affymetrix Santa Clara, CA, USA	Center for Inherited Disease Research, USA	University of Leipzig, Germany and ATLAS Biolabs GmbH, Berlin, Germany	Division of Endocrinology, Diabetes and Nutrition, University of Maryland School of Medicine	Broad Institute	General Clinical Research Center's Phenotyping/Genotyping Laboratory at Cedars-Sinai, USA	NHGRI	MRC Epidemiology Unit/ Sanger	Lille-France	NHGRI	Lille-France	MRC Epidemiology Unit/ Sanger	Kbiosciences	NHGRI	Broad Institute	Lille-France	Kbioscience	Broad Institute	Uppsala SNP Technology Platform	Kbioscience
Genotyping calling algorithm	Birdseed	Beadstudio	Illumina BeadStudio software	BRLMM	BRLMM	BRLMM	BRLMM	Beadstudio	BRLMM for 500K and Birdseed for SNP Array 6.0	Affymetrix = BRLMM; Taqman = manufacturer's software	Sequenom MassArray Typer 3.4	Illumina BeadStudio software	Sequenom MassArray Typer 3.4	n.a.	Illumina Beadsation Genotyping Solution	Sequenom MassArray Typer 3.4	7901 HT SDS 3.2 (Applied Biosystems)	n.a.	-	Sequenom MassArray Typer 3.4	Sequenom MassArray Typer 3.4	7900 HT SDS 3.2 (Applied Biosystems)	n.a.	Sequenom MassArray Typer 3.4	SNPstream GetGenos (Beckman Coulter)	n.a.
STUDY SAMPLE	**ARIC**	**BLSA**	**CHS-stage 1&2**	**CoLaus**	**DGI**	**Fenland**	**Framingham Offspring Cohort**	**FUSION**	**Sorbs**	**Amish (AFDS)**	**BotniaPPP**	**CHS-stage 3**	**DIAGEN**	**ELY**	**French Obese Adults**	**FUSIONs2**	**Haguenau cohort**	**Hertfordshire**	**Inter99**	**METSIM**	**NHANES**	**Obesity family relatives**	**RISC**	**Roche**	**ULSAM**	**WhiteHall II**
SAMPLE QC																										n.a.
Call rate [filter detail / N individuals excluded]	≥ 95% / 0	>98.5 % /9	>95% / 35	≥ 90% / 379	>95% /none	≥ 95% / 1	>97% / 119	>97.5% / 7	0.95		0.95	>95% / 35	0.95		0.98 [95/31]	0.95	0.96		0.95	0.95	0.988 [60%/215]	0.94		0.978 [60%/111]	0.95	
Heterozygosity [filter detail / N individuals excluded]	None	n.a.		n.a.	None	Heterozygosity < 0.28822 and > 0.27348 / 8	5 SD from mean (< 25.758% or > 29.958%) / 16	None	None																	
Ethnic outliers excluded	See below	Yes	African Americans excluded	n.a.	None	n.a.	None	None	Yes	none	none	African Americans excluded	none		41	none			none	none	none			none	none	
Other exclusions	Gender mismatch: X/Y checks (32); Inferred 1st degree relatives (83); Mismatch of 10 or more SNPs with SNPs previously genotyped on other platforms (297); Genetic outlier as assessed by Identity by State (IBS) using PLINK and >8 SD along any of the first 10 principal components in EIGENSTRAT with 5 iterations (331)	duplicates, gender mismatch	None	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	Parent-offspring combinations	Failed relatedness and duplicate check/ 43	> 1000 Mendelian errors / 1	None	Duplicates, gender mismatch	none	none	none	none		1 for cryptic relatedness	none			none	none	none			none	none	
Individuals for analysis	5083	857	1731	5435	1467	1384	6479	1234	941	up to 795	2,889		up to 1,171		663	up to 1,000	1,403		up to 5,778	up to 5,979	2,563	314		1,639	up to 949	
SNP QC (prior to imputation)																										
MAF [filter detail / N SNPs excluded]	1% / 142,918	>1% / 23,053	>1%	-	> 1% / 66,549	≥ 1% / 55,271	> 1% / 68,953	>1%	>1%	n.a.	0.01	>1%	0.01	n.a.	[0.05/14224]	0.01	[0.05/0]	n.a.		0.01	[0.01/0]	[0.05/0]	n.a.	[0.01/0]	0.01	n.a.
HWE P [filter detail / N SNPs excluded]	$>10^{-6}$ / 21,220	$>10^{-4}$ /470	$>10^{-5}$	$>10^{-7}$ / 35,417	$>10^{-6}$ / 5,775	$>10^{-6}$ / 3,690	$>10^{-6}$ / 20,999	$>10^{-6}$ /818	10-4	n.a.	0.000001	$>10^{-5}$	0.000001	n.a.	[0.001/888]	0.000001	[0.001/1]	n.a.		0.000001	0.000001	[0.001/0]	n.a.	0.000001	0.000001	n.a.
Call rate [filter detail / N SNPs excluded]	≥90% / 26,274	>99%/23,728	>95%	≥ 70%/ 157	≥ 95% / 34,761	≥ 90%/ 5,675	≥95% / 23,312	≥ 90% /544	≥95%	n.a.	95.%	>95%	90.%	n.a.	[95/7081]	95.%	[90/1]	n.a.		90.%	99.4 [95%/1]	[90/1]	n.a.	99.4 [95%/2]	95.%	n.a.
STUDY SAMPLE	**ARIC**	**BLSA**	**CHS-stage 1&2**	**CoLaus**	**DGI**	**Fenland**	**Framingham Offspring Cohort**	**FUSION**	**Sorbs**	**Amish (AFDS)**	**BotniaPPP**	**CHS-stage 3**	**DIAGEN**	**ELY**	**French Obese Adults**	**FUSIONs2**	**Haguenau cohort**	**Hertfordshire**	**Inter99**	**METSIM**	**NHANES**	**Obesity family relatives**	**RISC**	**Roche**	**ULSAM**	**WhiteHall II**
Other	No chromosome location (112) Significant differences in allele frequencies between batches (p<10-6) (21,395)		<=2 duplicate errors or Mendelian inconsistencies (for reference CEPH trios)		mapping to multiple locations (3,605 SNPs)		-	NMI or duplicate pair discrepancies <= 3	-	None		<=2 duplicate errors or Mendelian inconsistencies (for reference CEPH trios)					1					1				
SNP number in QC'd dataset	704588	514278	329327	390631	389878	362059	434,286 / 115,495	306791	909622	up to 795	22	329327			278086		8				31	8		35	3	
IMPUTATION STATS																										
Imputation software	MACH (v1.0.16)	MACH	BIMBAM10 v0.95	IMPUTE (v0.2.0, genotyped SNPs used where available)	MACH	IMPUTE (v0.4.2, genotyped SNPs used where available)	MACH	MACH	Impute			BIMBAM10 v0.95			IMPUTE v0.3.2											
Imputation quality metrics	r2hat>0.3	r2hat > 0.3	observed/expected variance ratio >0.3	proper-info ≥ 0.40	r2hat>0.3	proper-info ≥ 0.40	r2hat > 0.3	r2hat>0.3	Proper-info > 0.4			observed/expected variance ratio >0.3			proper_info > 0.4											
Other SNP QC filters applied?	Measured SNPs used for imputation were restricted to have: MAF > 1% >95% complete HWE $P > 10^{-5}$	MAF ≥ 1%	dosage variance >0.01	MAF ≥ 1%	MAF ≥ 1%	MAF ≥ 1%	MAF > 1%, average dose >=1%	MAF ≥ 1%	-			dosage variance >0.01			n/a											
DATA ANALYSIS																										
Number of SNPs in analysis	2,557,232	2,467,876	2,165,039	2,557,249	2,411,071	2,555,899	2,436,797	2,556,824	1,983,879		22	2,165,039		n.a.	for G120 83/68		8/0	n.a.	8		31/0	8/0	n.a.	35/0		n.a.
Trait transformation 2 hour GLUCOSE	none	none	none	none	none	none	none	none	none	none	none	none	none	none	none	none	none	none	none	none	none	none	none	none	none	none

Supplementary Table 1. Cohort and study characteristics and details of analysis metrics and methods

	discovery cohorts									replication cohorts															
STUDY SAMPLE	**ARIC**	**BLSA**	**CHS-stage 1&2**	**CoLaus**	**DGI**	**Fenland**	**Framingham Offspring Cohort**	**FUSION**	**Sorbs**	**Amish (AFDS)**	**BotniaPPP**	**CHS-stage 3**	**DIAGEN**	**ELY**	**French Obese Adults**	**FUSIONs2**	**Haguenau cohort**	**Hertfordshire**	**Inter99**	**METSIM**	**NHANES**	**Obesity family relatives**	**RISC**	**Roche**	**ULSAM**	**WhiteHall II**
Adjustments	gender, age, center, +/- BMI	age, sex, and PC, +/- BMI	age, sex, study site +/- BMI	gender, age, +/- BMI	age, age^2, gender, clinical site, glucose type, insulin type, +/- BMI	gender, age, +/- BMI	gender specific residuals adjusted for age and age^2, +/- BMI	age, age^2, gender, birth province, study, +/- BMI	age, sex, +/-BMI, genomic control (whole population isolate sample used)		age, sex, (+/- BMI, +/- fasting glucose)	age, sex, study site +/- BMI	age, sex, (+/- BMI, +/- fasting glucose)	age, sex, (+/- BMI, +/- fasting glucose)	age, sex, (+/- BMI, +/- fasting glucose)	age, age^2,sex, (+/- BMI and +/- fasting glucose)	gender, age, BMI, fasting glucose, intra-uterin developmment	age, sex, (+/- BMI, +/- fasting glucose)	age, sex, +/- BMI, +/- fasting glucose	age, age^2,sex, (+/- BMI and +/- fasting glucose)	age, sex, (+/- BMI and +/- fasting glucose)	age, sex, (+/- BMI, +/- fasting glucose)	age, sex, centre (+/- BMI, +/- fasting glucose)	age, sex, (+/- BMI and +/- fasting glucose)	age, sex, (+/- BMI and +/- fasting glucose)	age, sex, (+/- BMI and +/- fasting glucose)
Analysis method	linear regression (additive model)	linear regression	linear regression	linear regression (additive model)	linear regression (additive model)	linear regression (additive model)	linear mixed effect models	linear regression	linear regression (additive model)		Linear regression, additive genetic model	linear regression	Linear regression, additive genetic model	Linear regression (additive model)	F-test	Linear regression, additive genetic model	F-test	Linear regression (additive model)	Linear regression (additive model)	Linear regression, additive genetic model	GLM	mixed model	Linear regression (additive model)	GLM	Linear regression (additive model)	Linear regression (additive model)
Software for analysis	Mach2qtl (V104)	Merlin	R	SNPtest	PLINK	SNPtest	LMEKIN (R package)	Merlin	SNPTEST		PLINK	R	Merlin	Stata 10.1	SNPTEST v1.1.4	Merlin	SNPTEST v1.1.4	Stata 10.1	R	Merlin	SAS 9.1.3	R	Stata 10.1	SAS 9.1.3	Stata 10.1	Stata 10.1
Genomic Control Lambda (2h glucose)		1.04	1.01	1.009	1.005	1.0155		1.008	1 (Lambda GC used as baseline adjustment)																	
STUDY SAMPLE	**ARIC**	**BLSA**	**CHS-stage 1&2**	**CoLaus**	**DGI**	**Fenland**	**Framingham Offspring Cohort**	**FUSION**	**Sorbs**	**Amish (AFDS)**	**BotniaPPP**	**CHS-stage 3**	**DIAGEN**	**ELY**	**French Obese Adults**	**FUSIONs2**	**Haguenau cohort**	**Hertfordshire**	**Inter99**	**METSIM**	**NHANES**	**Obesity family relatives**	**RISC**	**Roche**	**ULSAM**	**WhiteHall II**
REFERENCES																										
Reference cohort	2	4		8	10			12	-					18	19		21	22	23		29	24	25	26	27	28
Reference GWAS		5		9	10			12	-																	
Website	http://www.csccunc.edu/aric/	http://www.grc.nia.nih.gov/branches/blsa/blsa.htm	http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000007.v2.p1		www.broad.mit.edu/diabetes	http://www.mrc-epid.cam.ac.uk/Studies/Fenland/	http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000007.v2.p1	http://fusion.sph.umich.edu	http://innere.uni klinikum-leipzig.de/_forschung/schwerpunkte/sorbs.html			http://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs000007.v2.p1		http://www.mrc-epid.cam.ac.uk/Studies/Ely/				http://www.mrc.soton.ac.uk/	http://www.hagedorn.dk/documents/article_page/document/Dep_521.asp		http://www.cdc.gov/nchs/nhanes.htm		http://www.egir.org/egirrisc/		http://www.pubcare.uu.se/ULSAM	http://www.ucl.ac.uk/whitehallII/

1 Pankow, J.S. et al. Cardiometabolic risk in impaired fasting glucose and impaired glucose tolerance: the Atherosclerosis Risk in Communities Study. Diabetes Care 30, 325-31

2 The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. The ARIC investigators. Am J Epidemiol 129, 687-702 (1989).

3 Carlson, O.D. et al. Contribution of nonesterified fatty acids to insulin resistance in the elderly with normal fasting but diabetic 2-hour postchallenge plasma glucose levels:

4 Shock, N.W. et al. Normal Human Aging: The Baltimore Longitudinal Study of Aging. (NIH publ. no. 84-hyphen]2450) (1984).

5 Tanaka, T. et al. Genome-wide association study of vitamin B6, vitamin B12, folate, and homocysteine blood concentrations. Am J Hum Genet 84, 477-82 (2009).

6 Cushman, M., Cornell, E.S., Howard, P.R., Bovill, E.G. & Tracy, R.P. Laboratory methods and quality assurance in the Cardiovascular Health Study. Clin Chem 41, 264-70 (1995).

7 Smith, N.L. et al. Fasting and 2-hour postchallenge serum glucose measures and risk of incident cardiovascular events in the elderly: the Cardiovascular Health Study. Arch Intern Med 162, 209-16 (2002)

8 Firmann, M. et al. The CoLaus study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. BMC Cardiovasc Disord 8, 6 (2008)

9 Prokopenko, I. et al. Variants in MTNR1B influence fasting glucose levels. Nat Genet 41, 77-81 (2009).

10 Saxena, R. et al. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. Science 316, 1331-6 (2007).

11 Herbert, V., Lau, K.S., Gottlieb, C.W. & Bleicher, S.J. Coated charcoal immunoassay of insulin. J Clin Endocrinol Metab 25, 1375-84 (1965).

12 Scott, L.J. et al. A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants. Science 316, 1341-5 (2007).

13 Werner, M., Tonjes, A., Stumvoll, M., Thiery, J. & Kratzsch, J. Assay-dependent variability of serum insulin levels during oral glucose tolerance test: influence on reference intervals for insulin and on cut-off values for insulin sensitivity indices. Clin Chem Lab Med 46, 240-6 (2008).

14- Diabetes Genetics Initiative of Broad, Lund, Novartis et al. Genome-wide association analysis identifies loci for type 2 diabetes and triglyceride levels. Science 316, 1331-6 (2007).

15- Leger, J. et al. Reduced final height and indications for insulin resistance in 20 year olds born small for gestational age: regional cohort study. Bmj 315, 341-7 (1997).

16- Balkau, B. et al. Physical activity and insulin sensitivity: the RISC study. Diabetes 57, 2613-8 (2008).

17- Zethelius, B., Byberg, L., Hales, C.N., Lithell, H. & Berne, C. Proinsulin and acute insulin response independently predict Type 2 diabetes mellitus in men--report from 27 years of follow-up study. Diabetologia 46, 20-6 (2003).

18- Forouhi, N.G., Luan, J., Hennings, S. & Wareham, N.J. Incidence of Type 2 diabetes in England and its association with baseline impaired fasting glucose: the Ely study 1990-2000. Diabet Med 24, 200-7 (2007).

19- Hager, J. et al. A genome-wide scan for human obesity genes reveals a major susceptibility locus on chromosome 10. Nat Genet 20, 304-8 (1998).

20-Kjems, L.L. et al. Highly sensitive enzyme immunoassay of proinsulin immunoreactivity with use of two monoclonal antibodies. Clin Chem 39, 2146-50 (1993).

21- Jaquet, D., Collin, D., Levy-Marchal, C. & Czernichow, P. Adult height distribution in subjects born small for gestational age. Horm Res 62, 92-6 (2004).

22- Syddall, H.E. et al. Cohort profile: the Hertfordshire cohort study. Int J Epidemiol 34, 1234-42 (2005).

23- Jorgensen, T. et al. A randomized non-pharmacological intervention study for prevention of ischaemic heart disease: baseline results Inter99. Eur J Cardiovasc Prev Rehabil 10, 377-86 (2003).

24- Meyre, D. et al. A genome-wide scan for childhood obesity-associated traits in French families shows significant linkage on chromosome 6q22.31-q23.2. Diabetes 53, 803-11 (2004).

25- Hills, S.A. et al. The EGIR-RISC STUDY (The European group for the study of insulin resistance: relationship between insulin sensitivity and cardiovascular disease risk): I. Methodology and objectives. Diabetologia 47, 566-70 (2004).

26- Ai, M. et al. Glycated albumin and direct low density lipoprotein cholesterol levels in type 2diabetes mellitus. Clinica Chimica Acta In press(2009).

27- Hedstrand, H. A study of middle-aged men with particular reference to risk factors for cardiovascular disease. Ups J Med Sci Suppl 19, 1-61 (1975).

28- Marmot, M. & Brunner, E. Cohort Profile: the Whitehall II study. Int J Epidemiol 34, 251-6 (2005).

Supplementary Table 2. Meta-analysis of association results for 2-hr glucose across discovery and replication cohorts.

SNP	Chr	Position (NCBI B36) (bp)	Nearest Gene	Effect Allele/ non-effect allele	Effect allele frequency	Discovery (BMI-adj)				Replication (BMI-adj)				Discovery + Replication (BMI-adj)					Discovery + Replication				
						N	Effect	(SE)	*p* -value	N	Effect	(SE)	*p* -value	N	Effect	(SE)	*p* -value	*p* -value$_{het}$	N	Effect	(SE)	*p* -value	*p* -value$_{het}$
rs17187140	1	206,376,398	*PLXNA2*	a/g	0.1	13,563	0.15	0.037	$6.29x10^{-5}$	13,377	-0.04	0.029	0.12	26,940	0.03	0.023	0.21	0.015	26,453	0.03	0.023	0.18	0.011
rs1260326	**2**	**27,584,444**	***GCKR***	**t/c**	0.40	**15,234**	**0.09**	**0.019**	$\mathbf{1.53x10^{-6}}$	**23,166**	**0.06**	**0.014**	$\mathbf{5.33x10^{-6}}$	**38,400**	**0.07**	**0.011**	$\mathbf{7.05x10^{-11}}$	**0.092**	**37,928**	**0.07**	**0.011**	$\mathbf{3.0x10^{-10}}$	**0.1092**
rs4971652	2	50,245,662	*NRXN1*	a/g	0.84	15,184	0.10	0.026	$2.20x10^{-4}$	12,173	0.01	0.027	0.82	27,357	0.05	0.019	$5.53x10^{-3}$	0.19	26,873	0.05	0.019	$4.21x10^{-3}$	0.093
rs12618178	2	54,908,792	*?*	a/c	0.20	15,234	-0.09	0.024	$1.04x10^{-4}$	14,354	0.01	0.022	0.63	29,588	-0.04	0.016	0.023	0.011	29,129	-0.04	0.016	0.014	$8.94x10^{-3}$
rs7604361	2	106,068,242	*(C2orf40)*	t/g	0.01	12,131	0.49	0.116	$2.71x10^{-5}$	9,707	0.03	0.107	0.77	21,838	0.24	0.079	$2.23x10^{-3}$	0.012	21,880	0.23	0.079	$4.14x10^{-3}$	0.011
rs16847412	2	142,335,384	*LRP1B*	t/c	0.93	15,234	-0.14	0.032	$2.33x10^{-5}$	17,104	-0.03	0.024	0.22	32,338	-0.07	0.019	$4.56x10^{-4}$	0.05	32,382	-0.07	0.020	$6.12x10^{-4}$	0.027
rs1955086	2	222,400,290	*(EPHA4)*	t/c	0.75	15,234	-0.08	0.023	$2.22x10^{-4}$	21,758	0.00	0.014	0.73	36,992	-0.03	0.012	0.025	0.11	36,542	-0.03	0.012	0.028	0.18
rs6726280	2	230,201,928	*DNER*	a/c	0.17	15,234	0.12	0.027	$6.71x10^{-6}$	23,448	0.01	0.016	0.71	38,682	0.04	0.014	$8.35x10^{-3}$	$1.39x10^{-3}$	38,202	0.04	0.014	$9.40x10^{-3}$	$3.24x10^{-4}$
rs12374129	3	78,626,542	*(ROBO1)*	t/c	0.15	15,234	0.09	0.023	$2.55x10^{-4}$	12,239	-0.02	0.023	0.42	27,473	0.03	0.016	0.049	0.17	27,297	0.04	0.016	0.018	0.26
rs2877716	**3**	**124,577,141**	***ADCY5***	**t/c**	**0.23**	**15,214**	**-0.10**	**0.022**	$\mathbf{6.26x10^{-6}}$	**29,483**	**-0.09**	**0.013**	$\mathbf{1.21x10^{-11}}$	**44,697**	**-0.09**	**0.011**	$\mathbf{4.19x10^{-16}}$	$\mathbf{5.85x10^{-8}}$	**44,225**	**-0.09**	**0.011**	$\mathbf{7.41x10^{-16}}$	$\mathbf{3.17x10^{-7}}$
rs9845279	3	158,795,136	*(C3orf55)*	c/g	0.56	12,909	-0.10	0.026	$9.46x10^{-5}$	12,017	0.00	0.018	0.99	24,926	-0.03	0.015	0.023	$1.57x10^{-4}$	24,438	-0.03	0.015	0.022	$2.97x10^{-4}$
rs309795	4	177,703,271	*(VEGFC)*	a/c	0.43	15,234	-0.09	0.019	$2.22x10^{-6}$	14,529	0.01	0.017	0.44	29,763	-0.03	0.013	$9.44x10^{-3}$	$1.30x10^{-4}$	29,284	-0.03	0.013	0.02	$1.25x10^{-4}$
rs10037968	5	101,582,380	*(SLCO4C1)*	t/c	0.99	15,234	0.19	0.037	$3.31x10^{-7}$	21,689	0.03	0.021	0.10	36,923	0.07	0.019	$7.49x10^{-5}$	$1.79x10^{-3}$	36,423	0.07	0.019	$2.86x10^{-4}$	$4.05x10^{-3}$
rs13265179	8	9,232,104	*PPP1R3B*	a/c	0.10	15,234	-0.11	0.028	$1.18x10^{-4}$	6,958	-0.09	0.049	0.064	22,192	-0.10	0.024	$2.06x10^{-5}$	0.21	22,023	-0.11	0.025	$1.69x10^{-5}$	0.12
rs12545656	8	99,548,888	*STK3*	a/g	0.93	15,234	-0.19	0.043	$1.28x10^{-5}$	14,533	-0.01	0.037	0.85	29,767	-0.08	0.028	$2.71x10^{-3}$	$9.77x10^{-3}$	29,288	-0.08	0.029	$4.63x10^{-3}$	$4.06x10^{-3}$
rs2439649	9	110,915,284	*C9orf5*	a/g	0.58	15,234	-0.07	0.019	$2.22x10^{-4}$	14,053	0.00	0.018	0.86	29,287	-0.03	0.013	$7.87x10^{-3}$	0.023	28,796	-0.04	0.013	$6.26x10^{-3}$	0.013
rs12243326	**10**	**114,778,805**	***TCF7L2***	**t/c**	**0.79**	**15,215**	**-0.13**	**0.022**	$\mathbf{1.20x10^{-9}}$	**23,351**	**-0.05**	**0.017**	$\mathbf{1.27x10^{-3}}$	**38,566**	**-0.08**	**0.013**	$\mathbf{4.23x10^{-10}}$	$\mathbf{1.08x10^{-3}}$	**38,078**	**-0.07**	**0.013**	$\mathbf{1.12x10^{-7}}$	$\mathbf{1.76x10^{-3}}$
rs12873155	13	31,609,703	*FRY*	t/c	0.40	15,234	0.09	0.019	$8.81x10^{-6}$	11,584	0.00	0.023	0.88	26,818	0.05	0.015	$1.05x10^{-3}$	0.075	26,358	0.04	0.015	$3.31x10^{-3}$	0.041
rs2585509	13	77,590,882	*(EDNRB)*	t/c	0.31	15,234	-0.08	0.020	$1.65x10^{-4}$	9,791	-0.02	0.029	0.53	25,025	-0.06	0.017	$5.86x10^{-4}$	0.23	24,526	-0.06	0.017	$2.05x10^{-4}$	0.3
rs17271305	**15**	**60,120,272**	***VPS13C***	**a/g**	**0.58**	**15,234**	**-0.09**	**0.019**	$\mathbf{1.04x10^{-6}}$	**15,633**	**-0.05**	**0.015**	$\mathbf{1.58x10^{-3}}$	**30,867**	**-0.06**	**0.012**	$\mathbf{4.11x10^{-8}}$	**0.22**	**30,906**	**-0.06**	**0.012**	$\mathbf{1.30x10^{-7}}$	**0.075**
rs12448015	16	22,665,124	*(HS3ST2)*	a/g	0.97	15,234	-0.21	0.052	$7.42x10^{-5}$	8,575	-0.18	0.090	0.043	23,809	-0.20	0.045	$8.93x10^{-6}$	0.042	23,299	-0.20	0.046	$1.46x10^{-5}$	0.027
rs7184872	16	27,374,838	*(GTF3C1)*	t/g	0.84	15,234	-0.11	0.030	$3.01x10^{-4}$	23,660	0.01	0.016	0.59	38,894	-0.02	0.014	0.21	0.15	38,421	-0.02	0.014	0.11	0.098
rs1060253	16	86,423,639	*SLC7A5*	c/g	0.32	15,234	0.09	0.022	$5.08x10^{-5}$	14,598	-0.02	0.019	0.23	29,832	0.03	0.014	0.073	$8.41x10^{-4}$	29,345	0.01	0.015	0.33	$3.69x10^{-4}$
rs17426106	17	41,184,706	*CRHR1*	c/g	0.22	10,031	-0.11	0.026	$3.21x10^{-5}$	11,733	-0.01	0.029	0.69	21,764	-0.07	0.020	$8.34x10^{-4}$	0.012	21,278	-0.06	0.020	$1.10x10^{-3}$	0.026
rs9952194	18	55,862,008	*(PMAIP1)*	t/c	0.79	15,234	0.08	0.021	$9.33x10^{-5}$	11,443	0.01	0.023	0.78	26,677	0.05	0.016	$2.28x10^{-3}$	0.22	26,167	0.05	0.016	$8.54x10^{-4}$	0.16
rs12985777	19	2,219,055	*?*	t/c	0.26	15,200	0.07	0.022	$2.31x10^{-3}$	9,663	0.05	0.032	0.090	24,863	0.06	0.018	$5.19x10^{-4}$	0.59	24,368	0.06	0.019	$1.10x10^{-3}$	0.57
rs4804519	19	10,669,770	*QTRT1*	t/c	0.63	15,234	0.07	0.020	$3.31x10^{-4}$	12,987	0.01	0.022	0.65	28,221	0.04	0.015	$3.07x10^{-3}$	0.49	28,266	0.04	0.015	$3.34x10^{-3}$	0.59
rs10423928	**19**	**50,874,144**	***GIPR***	**a/t**	**0.18**	**11,268**	**0.15**	**0.032**	$\mathbf{3.33x10^{-6}}$	**30,620**	**0.09**	**0.013**	$\mathbf{2.30x10^{-11}}$	**41,888**	**0.09**	**0.012**	$\mathbf{1.98x10^{-15}}$	$\mathbf{1.85x10^{-5}}$	**41,099**	**0.08**	**0.012**	$\mathbf{3.20x10^{-12}}$	$\mathbf{8.21x10^{-5}}$
rs2822664	21	14,743,816	*SAMSN1*	a/g	0.97	12,130	-0.25	0.073	$6.53x10^{-4}$	10,242	-0.07	0.075	0.37	22,372	-0.16	0.052	$2.12x10^{-3}$	0.29	21,872	-0.14	0.053	$7.18x10^{-3}$	0.24

Chromosomal position is listed according to NCBI build 36 (hg18). The gene closest to the SNP is indicated, a gene name without parenthesis indicates that the lead SNP resides within the listed gene, whereas a gene in parenthesis indicates the closest gene to an intergenic SNP. Effect allele/non-effect allele are defined based on the positive strand of NCBI build 36 (hg18). Effect allele frequencies are from the HapMap phase II CEU sample. Results from the inverse-variance meta-analysis are presented for the discovery samples. A standard set of SNP proxies (with r^2>0.8 in HapMap phase II CEU samples were genotyped when the primary SNP failed in replication studies).*P* -value$_{het}$ is the *P* value for heterogeneity across joint discovery and replication samples based on the Q statistic.*ADCY5* and *GIPR* SNPs displayed evidence of heterogeneity, and may reflect a differential effect of these SNPs on study samples with primarily normal glucose tolerant (NGT) vs. impaired glucose tolerant (IGT) individuals. All analyses are adjusted for sex, age, study-specific covariates. BMI-adj: these analyses are adjusted for sex, age, study-specific covariates and body mass index. FG-adj: these analyses are adjusted for fasting glucose, sex, age, study-specific covariates.

Supplementary Table 2. Meta-analysis of association results for 2-hr glucose across discovery and replication cohorts.

			models with further adjustment for fasting glucose																	
SNP	Nearest Gene	Effect Allele/non-effect allele	Discovery (FG-adj, BMI-adj)				Replication (FG-adj, BMI-adj)				Discovery + Replication (FG-adj, BMI-adj)					Discovery + Replication (FG-adj)				
			N	Effect	(SE)	*p* -value	N	Effect	(SE)	*p* -value	N	Effect	(SE)	*p* -value	p-value$_{het}$	N	Effect	(SE)	*p* -value	p-value$_{het}$
rs17187140	*PLXNA2*	a/g	13,358	0.15	0.036	3.37×10^{-5}	13,939	-0.04	0.028	0.14	27,297	0.03	0.022	0.16	0.016	26,819	0.03	0.023	0.14	8.21×10^{-3}
rs1260326	***GCKR***	**t/c**	**15,029**	**0.12**	**0.018**	**3.77×10^{-11}**	**22,624**	**0.09**	**0.014**	**1.04×10^{-11}**	**37,653**	**0.10**	**0.011**	**9.23×10^{-21}**	**0.099**	**37,181**	**0.11**	**0.011**	**2.26×10^{-21}**	**0.10**
rs4971652	*NRXN1*	a/g	14,979	0.08	0.026	1.14×10^{-3}	11,658	0.01	0.026	0.76	26,637	0.05	0.018	0.011	0.26	26,673	0.05	0.018	0.011	0.16
rs12618178	*?*	a/c	15,029	-0.09	0.023	5.03×10^{-5}	13,840	0.01	0.021	0.56	28,869	-0.04	0.016	0.02	0.014	28,390	-0.04	0.016	0.015	8.37×10^{-3}
rs7604361	*(C2orf40)*	t/g	10,696	0.53	0.120	9.43×10^{-6}	10,803	0.06	0.105	0.56	21,499	0.27	0.079	7.74×10^{-4}	3.79×10^{-3}	21,016	0.24	0.080	3.32×10^{-3}	4.29×10^{-3}
rs16847412	*LRP1B*	t/c	15,029	-0.12	0.032	1.64×10^{-4}	17,087	-0.02	0.024	0.33	32,116	-0.06	0.019	2.41×10^{-3}	0.036	31,634	-0.06	0.019	3.78×10^{-3}	0.018
rs1955086	*(EPHA4)*	t/c	15,029	-0.08	0.022	2.38×10^{-4}	21,241	-0.01	0.014	0.62	36,270	-0.03	0.012	0.018	0.070	35,793	-0.02	0.012	0.037	0.11
rs6726280	*DNER*	a/c	15,029	0.11	0.026	3.45×10^{-5}	22,903	0.01	0.016	0.71	37,932	0.03	0.014	0.013	0.014	37,455	0.03	0.014	0.02	6.46×10^{-3}
rs12374129	*(ROBO1)*	t/c	15,029	0.07	0.023	1.98×10^{-3}	11,912	-0.02	0.022	0.38	26,941	0.02	0.016	0.12	0.27	26,889	0.03	0.016	0.072	0.42
rs2877716	***ADCY5***	**t/c**	**15,009**	**-0.08**	**0.022**	**2.24×10^{-4}**	**28,938**	**-0.07**	**0.013**	**1.65×10^{-8}**	**43,947**	**-0.07**	**0.011**	**1.68×10^{-11}**	**4.74×10^{-8}**	**43,480**	**-0.08**	**0.011**	**7.98×10^{-12}**	**2.14×10^{-7}**
rs9845279	*(C3orf55)*	c/g	12,704	-0.10	0.025	4.03×10^{-5}	12,596	-0.01	0.018	0.71	25,300	-0.04	0.015	7.14×10^{-3}	4.61×10^{-4}	25,342	-0.04	0.015	6.76×10^{-3}	9.44×10^{-4}
rs309795	*(VEGFC)*	a/c	15,029	-0.09	0.019	5.59×10^{-6}	12,891	0.01	0.017	0.49	27,920	-0.03	0.013	9.81×10^{-3}	1.06×10^{-4}	28,545	-0.03	0.013	0.017	2.09×10^{-4}
rs10037968	*(SLCO4C1)*	t/c	15,029	0.20	0.036	2.14×10^{-8}	21,129	0.03	0.021	0.094	36,158	0.08	0.018	2.17×10^{-5}	6.18×10^{-4}	35,674	0.07	0.018	4.91×10^{-5}	8.25×10^{-4}
rs13265179	*PPP1R3B*	a/c	15,029	-0.12	0.027	2.50×10^{-5}	6,745	-0.13	0.047	6.60×10^{-3}	21,774	-0.12	0.024	5.24×10^{-7}	0.18	21,815	-0.12	0.024	3.10×10^{-7}	0.13
rs12545656	*STK3*	a/g	15,029	-0.17	0.042	3.25×10^{-5}	13,999	-0.01	0.037	0.86	29,028	-0.08	0.028	4.29×10^{-3}	0.014	28,549	-0.08	0.028	5.07×10^{-3}	3.92×10^{-4}
rs2439649	*C9orf5*	a/g	15,029	-0.07	0.018	4.81×10^{-5}	13,507	0.00	0.017	0.97	28,536	-0.04	0.013	4.51×10^{-3}	5.62×10^{-3}	28,588	-0.04	0.013	4.58×10^{-3}	3.11×10^{-3}
rs12243326	***TCF7L2***	**t/c**	**15,010**	**-0.12**	**0.021**	**3.69×10^{-9}**	**22,790**	**-0.05**	**0.016**	**5.32×10^{-3}**	**37,800**	**-0.07**	**0.013**	**9.99×10^{-9}**	**3.16×10^{-3}**	**37,326**	**-0.08**	**0.013**	**1.17×10^{-10}**	**0.24**
rs12873155	*FRY*	t/c	15,029	0.08	0.019	7.09×10^{-6}	11,070	0.00	0.022	0.83	26,099	0.05	0.014	3.70×10^{-4}	0.12	25,628	0.05	0.015	8.20×10^{-4}	0.067
rs2585509	*(EDNRB)*	t/c	15,029	-0.06	0.020	9.72×10^{-4}	9,245	-0.01	0.028	0.75	24,274	-0.05	0.016	4.03×10^{-3}	0.27	23,788	-0.05	0.016	3.09×10^{-3}	0.24
rs17271305	***VPS13C***	**a/g**	**15,029**	**-0.11**	**0.018**	**8.52×10^{-9}**	**15,615**	**-0.05**	**0.014**	**9.97×10^{-5}**	**30,644**	**-0.07**	**0.011**	**4.33×10^{-11}**	**0.29**	**29,680**	**-0.07**	**0.011**	**8.41×10^{-11}**	**0.11**
rs12448015	*(HS3ST2)*	a/g	15,029	-0.19	0.051	2.35×10^{-4}	8,034	-0.15	0.086	0.082	23,063	-0.18	0.044	5.12×10^{-5}	0.15	22,621	-0.17	0.044	8.44×10^{-5}	0.12
rs7184872	*(GTF3C1)*	t/g	15,029	-0.11	0.029	7.72×10^{-5}	23,119	0.01	0.016	0.59	38,148	-0.02	0.014	0.15	0.084	37,193	-0.03	0.014	0.06	0.11
rs1060253	*SLC7A5*	c/g	15,029	0.09	0.021	1.25×10^{-5}	14,057	-0.05	0.019	8.10×10^{-3}	29,086	0.01	0.014	0.35	1.00×10^{-4}	28,131	0.02	0.014	0.23	8.07×10^{-5}
rs17426106	*CRHR1*	c/g	10,007	-0.11	0.025	2.01×10^{-5}	11,192	0.00	0.028	0.88	21,199	-0.06	0.019	1.16×10^{-3}	3.19×10^{-3}	20,235	-0.05	0.019	6.29×10^{-3}	0.021
rs9952194	*(PMAIP1)*	t/c	15,029	0.07	0.021	3.18×10^{-4}	10,902	0.01	0.022	0.55	25,931	0.05	0.015	2.26×10^{-3}	0.55	25,489	0.05	0.015	9.00×10^{-4}	0.50
rs12985777	*?*	t/c	14,995	0.08	0.022	1.18×10^{-4}	9,121	0.05	0.030	0.11	24,116	0.07	0.018	4.48×10^{-5}	0.37	23,153	0.07	0.018	5.28×10^{-5}	0.41
rs4804519	*QTRT1*	t/c	15,029	0.08	0.019	3.94×10^{-5}	12,979	0.01	0.021	0.58	28,008	0.05	0.014	6.32×10^{-4}	0.22	27,049	0.05	0.015	5.28×10^{-4}	0.21
rs10423928	***GIPR***	**a/t**	**11,066**	**0.16**	**0.030**	**1.04×10^{-7}**	**29,762**	**0.10**	**0.013**	**6.33×10^{-15}**	**40,828**	**0.11**	**0.012**	**2.56×10^{-20}**	**3.08×10^{-5}**	**40,354**	**0.10**	**0.012**	**5.943×10^{-21}**	**4.96×10^{-5}**
rs2822664	*SAMSN1*	a/g	11,928	-0.28	0.070	1.43×10^{-5}	10,815	-0.07	0.073	0.35	22,743	-0.18	0.050	3.20×10^{-4}	0.21	22,301	-0.17	0.051	6.00×10^{-4}	0.14

Supplementary Table 4. Association of rs10423928 [*GIPR*], rs17271305 [*VPS13C*] and rs2877716 [*ADCY5*] with insulinogenic index, AUC (area under the curve) insulin/ glucose, and 2h insulin (adjusted for 2h glucose) within MAGIC and meta-analysis across all studies.

	***GIPR* SNP rs10423928 A**				***ADCY5* SNP rs2877716 C**				***VPS13C* SNP rs17271305 G**			
Study sample	N	Per allele effect (SE) (BMI adj.)	*P* -value (BMI adj.)	*P* -value	N	Per allele effect (SE) (BMI adj.)	*P* -value (BMI adj.)	*P* -value	N	Per allele effect (SE) (BMI adj.)	*P* -value (BMI adj.)	*P* -value
Insulinogenic index (µU/mmol) [1]												
AMISH	674	-0.075 (0.073)	0.61	0.42	527**	-0.004 (0.067)	0.98	0.76	675	-0.142 (0.050)	0.16	0.11
BotniaPPP	4,241	-0.074 (0.018)	$4.5x10^{-5}$	$8.7x10^{-6}$	2,811**	-0.029 (0.028)	0.3	0.31	4,121***	0.014 (0.016)	0.4	0.37
DIAGEN	943	-0.077 (0.040)	0.057	0.066	922**	-0.005 (0.042)	0.99	0.98	-	-	-	-
Ely	1,306*	-0.127 (0.035)	$2.43x10^{-4}$	$7.82x10^{-5}$	1,360	-0.042 (0.030)	0.16	0.076	-	-	-	-
French Family Members	233	0.090 (0.112)	0.43	0.45	228	0.100 (0.126)	0.43	0.35	216	-0.080 (0.110)	0.44	0.45
French Haguenau	1,244	-0.003 (0.039)	0.94	0.9	1,243	-0.037 (0.037)	0.32	0.19	1,259	0.015 (0.032)	0.63	0.64
French Obese Adults	206	-0.196 (0.121)	0.107	0.07	-	-	-	-	-	-	-	-
Hertfordshire Study	996*	-0.067 (0.042)	0.11	0.12	977	-0.052 (0.037)	0.16	0.25	-	-	-	-
Inter99	5,016	-0.117 (0.023)	$2.68x10^{-7}$	$3.91x10^{-7}$	5,059	0.020 (0.021)	0.34	0.26	5,013	0.042 (0.019)	0.029	0.06
METSIM	4,998	-0.057 (0.018)	0.0013	$2.98x10^{-4}$	5,034**	-0.009 (0.020)	0.64	0.77	-	-	-	-
RISC	1,168	-0.063 (0.035)	0.072	0.027	1,164	-0.022 (0.033)	0.508	0.42	1,153	-0.002 (0.029)	0.94	0.85
ROCHE	545	-0.033 (0.063)	0.61	0.37	551	-0.011 (0.059)	0.85	0.74	551	-0.005 (0.052)	0.92	0.85
ULSAM	922	-0.104 (0.039)	0.007	0.02	910**	-0.029 (0.041)	0.48	0.6	912	0.031 (0.034)	0.36	0.59
Meta-analysis	22,492	-0.076 (0.009)	$1.00x10^{-17}$	$2.09x10^{-20}$	20,786	-0.011 (0.009)	0.23	0.22	13,900	0.024 (0.010)	0.013	0.020
AUC (area under the curve) insulin/ glucose (pmol/mmol) [2]												
AMISH	643	-0.0078 (0.037)	0.92	0.46	505	0.050 (0.036)	0.49	0.3	645	-0.0076 (0.026)	0.89	0.77
Botnia PPP	4,277	-0.050 (0.012)	3.1×10^{-5}	1.6×10^{-6}	2,811	-0.039 (0.018)	0.031	0.065	4,153***	0.0080 (0.011)	0.46	0.47
DIAGEN	950	0.039(0.026)	0.14	0.11	930	0.026 (0.028)	0.35	0.45	-	-	-	-
Ely	1,196*	-0.069 (0.023)	3.0×10^{-3}	2.6×10^{-4}	1,245	0.007 (0.020)	0.74	0.38	-	-	-	-
French Family members	272	-0.12 (0.084)	0.14	0.15	266	0 (0.095)	0.97	0.82	250	-0.020 (0.085)	0.84	0.86
French Haguenau	1,159	0.0090 (0.024)	0.71	0.7	1,159	0.032 (0.024)	0.17	0.49	1,173	0.022 (0.020)	0.27	0.31
French Obese Adults	237	-0.057 (0.093)	0.54	0.45	-	-	-	-	-	-	-	-
Hertfordshire	992**	-0.045 (0.030)	0.14	0.13	973	-0.046 (0.027)	0.084	0.2	-	-	-	-
Inter99	4,946	-0.10 (0.022)	4.7×10^{-6}	2.6×10^{-5}	4,984	-0.027 (0.020)	0.18	0.36	4,941	0.0080 (0.018)	0.66	1
METSIM	5,031	-0.038 (0.012)	2.1×10^{-3}	2.2×10^{-4}	5,066	-0.016 (0.014)	0.25	0.45	-	-	-	-
RISC	1,007	-0.073 (0.025)	4.1×10^{-3}	7.0×10^{-4}	1,004	0.0004 (0.024)	0.99	0.75	997	-0.017 (0.020)	0.42	0.32
ROCHE	571	-0.040 (0.038)	0.29	0.1	576	0.010 (0.036)	0.78	0.72	576	-0.048 (0.031)	0.12	0.31
ULSAM	928	-0.094 (0.025)	1.6×10^{-4}	1.4×10^{-3}	916**	-0.0002 (0.026)	0.99	0.81	918	-0.032 (0.022)	0.14	0.047
Meta-analysis	22,209	-0.051 (0.006)	$1.3x10^{-16}$	$3.7x10^{-20}$	20,435	0.010 (0.007)	0.16	0.19	13,653	-0.001 (0.007)	0.86	0.76
2h insulin (adjusted for 2h glucose) [3]												
AMISH	685	0.139 (0.045)	0.13	0.24	534**	0.17 (0.055)	0.13	0.091	688	-0.12 (0.033)	0.16	0.12
BLSA	460	-0.085 (0.056)	0.14	0.10	460	-0.006 (0.053)	0.91	0.93	460	-0.043 (0.042)	0.32	0.38
BotniaPPP	2,725	-0.067 (0.030)	0.028	0.013	2,699**	-0.11 (0.036)	$3.0x10^{-3}$	$3.06x10^{-3}$	4214***	-0.012 (0.013)	0.38	0.35
CHS-1	1,658	-0.081 (0.029)	$4.43x10^{-3}$	$3.08x10^{-3}$	1,658	-0.028 (0.025)	0.27	0.51	1,658	-0.065 (0.024)	$5.55x10^{-3}$	0.022
CHS-2	2,786	-0.060 (0.020)	$2.90x10^{-3}$	$1.60x10^{-3}$	-	-	-	-	-	-	-	-
DGI	-	-	-	-	1,045	-0.015 (0.057)	0.80	0.78	1,045	-0.033 (0.043)	0.45	0.58
DIAGEN	954	-0.062 (0.031)	0.047	0.041	934**	0.020 (0.033)	0.55	0.60	-	-	-	-
Ely	1,357*	-0.027 (0.024)	0.26	0.035	1,411	-0.0038 (0.021)	0.86	0.19	-	-	-	-
FHS	2,637	-0.055 (0.015)	$3.08x10^{-4}$	$3.79x10^{-5}$	2,618	-0.016 (0.014)	0.28	0.21	2,637	-0.012 (0.012)	0.32	0.21
FUSION	581	-0.026 (0.039)	0.51	0.57	581	-0.043 (0.041)	0.30	0.24	581	-0.059 (0.032)	0.066	0.043
Fusion Stage 2	286	-0.024 (0.046)	0.60	0.89	271	0.025 (0.055)	0.66	0.83	-	-	-	-
Hertfordshire	1071*	-0.073 (0.038)	0.05	0.046	1,048	-0.037 (0.033)	0.26	0.31	-	-	-	-
Inter99	5,349	-0.034 (0.016)	0.036	0.024	5,388	-0.059 (0.015)	$9.86x10^{-5}$	$5.96x10^{-4}$	5,342	-0.048 (0.014)	$4.19x10^{-4}$	$9.38x10^{-5}$
METSIM	5,055	-0.020 (0.015)	0.18	0.037	5,094**	-0.053 (0.017)	$1.80x10^{-3}$	$2.89x10^{-3}$	-	-	-	-
NHANES	528	-0.091 (0.040)	0.021	0.011	525	-0.080 (0.039)	0.039	0.043	528	-0.029 (0.033)	0.82	0.31
RISC	1,141	-0.036 (0.034)	0.24	0.11	1,136	-0.010 (0.032)	0.56	0.49	1,123	-0.057 (0.028)	0.041	0.023
ROCHE	583	-0.084 (0.049)	0.086	0.047	588	0.036 (0.046)	0.44	0.47	588	-0.091 (0.039)	0.021	0.029
Sorbs	-	-	-	-	651	-0.068 (0.048)	0.17	0.19	651	-0.029 (0.037)	0.46	0.59
ULSAM	937	-0.064 (0.029)	0.028	0.046	925**	-0.032 (0.030)	0.29	0.55	927	-0.086 (0.025)	$7.32x10^{-4}$	$1.75x10^{-4}$
Whitehall	3,411	-0.042 (0.019)	0.025	$2.27x10^{-3}$	3,421	-0.023 (0.017)	0.16	0.19	3,400	-0.033 (0.015)	0.028	0.041
Meta-analysis	32,204	-0.044 (0.006)	$1.99x10^{-13}$	$3.67x10^{-16}$	30,987	-0.029 (0.006)	$1.43x10^{-6}$	$3.09x10^{-6}$	23,842	-0.037 (0.006)	$7.45x10^{-11}$	$2.58x10^{-10}$

*rs11672660 proxy for *GIPR* SNP; **rs11708067 proxy for ADCY5 SNP; ***rs10519116 proxy for VPS13C SNP

1- Additive effect of the risk allele on insulinogenic index using study specific adjustments (including gender and age) with and without BMI adjustment. All outcomes were transformed using the natural logarithm.

2- Additive effect on AUC (area under the curve) insulin/ glucose using study specific adjustments (including gender and age) with and without BMI adjustment. All outcomes were transformed using the natural logarithm

3- Additive effect of risk alleles on 2h insulin (adjusted for 2h glucose) using study specific adjustments (including gender and age) with and without BMI adjustment. All outcomes were transformed using the natural logarithm