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Replication of Genome-Wide Association Signals in UK Samples Reveals Risk Loci for Type 2 Diabetes

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The molecular mechanisms involved in the development of type 2 diabetes are poorly understood. Starting from genome-wide genotype data for 1924 diabetic cases and 2938 population controls generated by the Wellcome Trust Case Control Consortium, we set out to detect replicated diabetes association signals through analysis of 3757 additional cases and 5346 controls and by integration of our findings with equivalent data from other international consortia. We detected diabetes susceptibility loci in and around the genes *CDKAL1*, *CDKN2A/CDKN2B*, and *IGF2BP2* and confirmed the recently described associations at *HHEX/IDE* and *SLC30A8*. Our findings provide insight into the genetic architecture of type 2 diabetes, emphasizing the contribution of multiple variants of modest effect. The regions identified underscore the importance of pathways influencing pancreatic beta cell development and function in the etiology of type 2 diabetes.

The pathophysiological basis of type 2 diabetes (T2D) remains unclear despite its growing global importance (*1*). Candidate gene and positional cloning efforts have suggested many putative susceptibility variants, but unequivocal replications are so far limited to variants in just three genes: *PPARG*, *KCNJ11*, and *TCF7L2* (*2*–*4*).

Improved understanding of the correlation between genetic variants [linkage disequilibrium (LD)], allied to advances in genotyping technology, have enabled systematic searches for disease-associated common variants on a genome-wide scale. The Wellcome Trust Case Control Consortium (WTCCC) recently completed such a genome-wide association (GWA) scan in 1924 T2D cases and 2938 population controls from the United Kingdom, using the Affymetrix GeneChip Human Mapping 500 k Array Set (*5*). The strongest association signals genome-wide were observed for single-nucleotide polymorphisms (SNPs) in *TCF7L2*. [For example, for rs7901695, odds ratio (OR) = 1.37, 95% confidence interval (CI) = 1.25–1.49, and $P = 6.7 \times 10^{-13}$.] The other known T2D susceptibility variants were detected with effect sizes consistent with previous reports (*2*, *3*).

Here, we describe how integration of data from the WTCCC scan and our own replication studies with similar information generated by the Diabetes Genetics Initiative (DGI) (*6*) and the Finland–United States Investigation of NIDDM Genetics (FUSION) (*7*) has identified several additional susceptibility variants for T2D.

In the WTCCC study, analysis of 490,032 autosomal SNPs in 16,179 samples yielded 459,448 SNPs that passed initial quality control (*5*). We considered only the 393,453 autosomal SNPs with minor allele frequency (MAF) exceeding 1% in both cases and controls and no extreme departure from Hardy-Weinberg equilibrium ($P < 10^{-4}$ in cases or controls) (*8*). This T2D-specific data set shows no evidence of substantial confounding from population substructure and genotyping biases (*8*).

To distinguish true associations from those reflecting fluctuations under the null or residual errors arising from aberrant allele calling, we first submitted putative signals from the WTCCC study to additional quality control, including cluster-plot visualization and validation genotyping on a second platform (*8*). Next, we attempted replication of selected signals in up to 3757 additional cases and 5346 controls (replication sets RS1 to RS3). RS1 comprised 2022 cases and 2037 controls from the U.K. Type 2 Diabetes Genetics Consortium collection (UKT2DGC) (all from Tayside, Scotland). RS2 included 632 additional T2D cases and 1750 population controls from the Exeter Family Study of Child Health (EFSOCH). A subset of SNPs were typed in RS3, comprising a further 1103 cases and 1559 controls from the UKT2DGC (table S1).

The first wave of validated SNPs sent for replication was selected from the 30 SNPs, in nine distinct chromosomal regions (excluding *TCF7L2*), which had, in the WTCCC scan alone,

attained the most extreme ($P < 10^{-5}$) significance values on Cochran-Armitage tests of association. Genotyping of 21 representative SNPs generated evidence of replication ($P < 0.05$) for three of these nine regions (Table 1 and table S2).

Rs8050136 [mapping to the *FTO* (fat mass and obesity-associated) gene region on chr16] was among a cluster of SNPs generating the strongest evidence for association outside *TCF7L2* in the original scan [risk allele OR = 1.27 (1.16–1.37), $P = 2.0 \times 10^{-8}$] (fig. S1). This SNP showed strong replication [OR = 1.22 (1.12–1.32), $P = 5.4 \times 10^{-7}$]. As we recently reported (*9*), this effect on T2D risk is mediated through a primary effect on adiposity, and adjustment for body mass index (BMI) abolishes the T2D association.

Replication was also obtained for SNPs within the *CDKAL1* locus on chromosome 6, including rs9465871 and rs10946398. Although rs9465871 generated the stronger signal in the WTCCC scan, replication at this SNP was modest ($P = 0.023$). The replication signal at rs10946398 was more striking [OR = 1.14 (1.07–1.22), $P = 8.4 \times 10^{-5}$] (Table 1 and table S2). Consistent evidence of association is provided by the DGI ($P = 4.1 \times 10^{-4}$ at rs7754840) and FUSION groups ($P = 9.5 \times 10^{-3}$ at rs471253) (Table 1 and table S3) (*6*, *7*), both SNPs being strong ($r^2 > 0.99$) proxies for rs10946398. Across all studies, combined evidence for association at *CDKAL1* is compelling ($P \sim 4.1 \times 10^{-11}$).

All associated SNPs map to a large (90 kb) intron within *CDKAL1* (Fig. 1). Flanking recombination hotspots define a 200-kb interval likely to contain the etiological variant(s). *CDKAL1* [cyclin-dependent kinase 5 (CDK5) regulatory subunit associated protein 1–like 1] encodes a 579-residue, 65-kD protein of unknown function. We have detected expression of *CDKAL1* mRNA in human pancreatic islet and skeletal muscle (fig. S2). CDKAL1 shares considerable protein domain and amino acid homology with CDK5 regulatory subunit associated protein 1 (CDK5RAP1), a known inhibitor of CDK5 activation. CDK5 has been implicated in the regulation of pancreatic beta cell function through formation of p35/CDK5 complexes that down-regulate insulin expression (*10*, *11*).

The third replicated association maps to the *HHEX* (homeobox, hematopoietically expressed) gene region on chromosome 10. This gene showed strong association in the WTCCC scan [rs5015480: risk allele OR = 1.22 (CI, 1.12–1.33), $P = 5.4 \times 10^{-6}$] and is a powerful biological candidate (*12*, *13*). We could not optimize a replication assay for rs5015480 but observed evidence for replication at a perfect proxy, rs1111875 [risk allele OR = 1.08 (CI, 1.01–1.15), $P = 0.02$] (Table 1, tables S2 and S3). Both DGI and FUSION studies showed modest but consistent association signals generating strong combined evidence ($P \sim 5.7 \times 10^{-10}$) for a role in T2D susceptibility (Table 1 and table S3). A fourth genome-wide association scan, in French subjects, recently yielded independent evidence for a T2D signal in this region (*14*). The signal resides within an extended (295 kb) region of LD containing not only *HHEX* [highly expressed in fetal and adult pancreas (fig. S2)] but also the genes encoding kinesin-interacting factor (*KIF11*) and insulin-degrading enzyme (*IDE*) (fig. S3). *IDE* represents a second strong biological candidate given postulated effects on both insulin signaling and islet function and data from rodent models (*15*–*17*).

Of the remaining regions selected in the first wave, none showed any evidence of replication in U.K. samples (table S2), and for none was there strong support from the DGI and FUSION scans.

The relatively strict thresholds imposed for SNP selection in the first wave (i.e., point-wise

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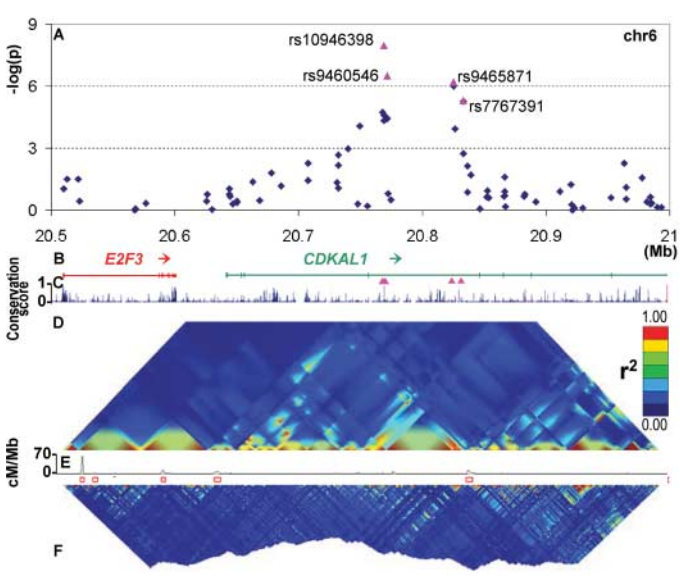

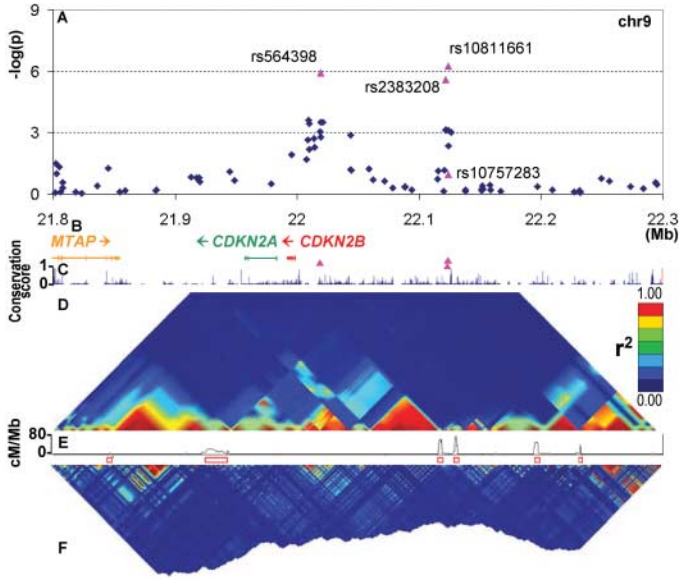

Fig. 1. (**left**) Overview of *CDKAL1* signal region. (**A**) Plot of –log(*P* values) for T2D (Cochran-Armitage test for trend) against chromosome position in Mb. Blue diamonds represent primary scan results and pink triangles denote meta-analysis results across all UK samples. (**B**) Genomic location of genes showing intron and exon structure (NCBI Build 35). Pink triangles show position of replication SNPs relative to gene structure. (**C**) MULTIZ (*24*) vertebrate alignment of 17 species showing evolutionary conservation. (**D**) GoldSurfer2 (*25*) plot of linkage disequilibrium (r^2) for SNPs genotyped in WTCCC scan (passing T2D-specific quality control) in WTCCC T2D cases. (**E**) Recombination rate given as cM/MB. Red boxes represent recombination hotspots (*26*). (**F**) GoldSurfer2 plot of linkage disequilibrium (r^2) for all HapMap (haplotype map of the human genome) SNPs across the region (HapMap CEU data) (*27*). **Fig. 2.** (**right**) Overview of chr9 signal region. Panel layout as in Fig. 1.

Table 1. Confirmed T2D susceptibility variants. Representative SNPs are shown for each signal with ORs and 95% CIs reported (for the Cochran-Armitage 1 df test) with respect to the risk allele (denoted in bold, with the ancestral allele underlined where known). SNPs selected for inclusion are those with the strongest evidence for association in the U.K. data sets (except in the case of *TCF7L2*, where, to maximize consistency across the data sets, rs7901695 is presented). In the case of *HHEX*, the U.K. meta-analysis combines data from rs5015480 and rs1111875 (r^2 = 1 in HapMap CEU). Because DGI and FUSION had not typed the identical SNPs in all samples, results shown for those studies feature the SNP generating the strongest association: In all cases, these were SNPs in strong LD (minimum r^2 0.95, except *TCF7L2*) and with consistent direction of effect with the SNP reported in the U.K. data (see table S3 for details). The use of different SNPs may result in slightly different estimates of *P* values and OR between the three studies. Combined estimates of the ORs were calculated by weighting the logORs of each study by the inverse of their variance.

rs	chr	position	A1	A2	Region	WTCCC 1924 cases 2938 controls OR (95% CI)	P_{add}	Replication meta-analysis 3757 cases 5346 controls OR (95% CI)	P_{add}	All UK sample meta-analysis 5681 cases 8284 controls OR (95% CI)	P_{add}	DGI 6529 cases 7252 controls OR (95% CI)	P_{add}	FUSION 2376 cases 2432 controls OR (95% CI)	P_{add}	All combined 14,586 cases 17,968 controls OR (95% CI)	P_{add}
rs8050136	16	52373776	**A**	C	*FTO*	1.27 (1.16–1.37)	2.0×10^{-8}	1.22 (1.12–1.32)	5.4×10^{-7}	1.23 (1.18–1.32)	7.3×10^{-14}	1.03 (0.91–1.17)	0.25	1.11 (1.02–1.20)	0.017	1.17 (1.12–1.22)	1.3×10^{-12}
rs10946398	6	20769013	A	**C**	*CDKAL1*	1.20 (1.10–1.31)	2.5×10^{-5}	1.14 (1.07–1.22)	8.3×10^{-5}	1.16 (1.10–1.22)	1.3×10^{-8}	1.08 (1.03–1.14)	2.4×10^{-3}	1.12 (1.03–1.22)	9.5×10^{-3}	1.12 (1.08–1.16)	4.1×10^{-11}
rs5015480	10	94455539	**C**	T	*HHEX*	1.22 (1.12–1.33)	5.4×10^{-6}	–	–	1.13 (1.07–1.19)	4.6×10^{-6}	1.14 (1.06–1.22)	1.7×10^{-4}	1.10 (1.01–1.19)	0.025	1.13 (1.08–1.17)	5.7×10^{-10}
rs1111875	10	94452862	**C**	T	*HHEX*	–	–	1.08 (1.01–1.15)	0.020								
rs10811661	9	22124094	C	**T**	*CDKN2B*	1.22 (1.09–1.37)	7.6×10^{-4}	1.18 (1.08–1.28)	1.7×10^{-4}	1.19 (1.11–1.28)	4.9×10^{-7}	1.20 (1.12–1.28)	5.4×10^{-8}	1.20 (1.07–1.36)	2.2×10^{-3}	1.20 (1.14–1.25)	7.8×10^{-15}
rs564398	9	22019547	C	**T**	*CDKN2B*	1.16 (1.07–1.27)	3.2×10^{-4}	1.12 (1.05–1.19)	8.6×10^{-4}	1.13 (1.08–1.19)	1.3×10^{-6}	1.05 (0.94–1.17)	0.5	1.13 (1.01–1.27)	0.039	1.12 (1.07–1.17)	1.2×10^{-7}
rs4402960	3	186994389	G	**T**	*IGF2BP2*	1.15 (1.05–1.25)	1.7×10^{-3}	1.09 (1.01–1.16)	0.018	1.11 (1.05–1.16)	1.6×10^{-4}	1.17 (1.11–1.23)	1.7×10^{-9}	1.18 (1.08–1.28)	2.4×10^{-4}	1.14 (1.11–1.18)	8.6×10^{-16}
rs13266634	8	118253964	**C**	T	*SLC30A8*	1.12 (1.02–1.23)	0.020	1.12 (1.04–1.19)	1.2×10^{-3}	1.12 (1.05–1.18)	7.0×10^{-5}	1.07 (1.00–1.16)	0.047	1.18 (1.09–1.29)	7.0×10^{-5}	1.12 (1.07–1.16)	5.3×10^{-8}
rs7901695	10	114744078	**C**	T	*TCF7L2*	1.37 (1.25–1.49)	6.7×10^{-13}	–	–	–	–	1.38 (1.31–1.46)	2.3×10^{-31}	1.34 (1.21–1.49)	1.4×10^{-8}	1.37 (1.31–1.43)	1.0×10^{-48}
rs5215	11	17365206	**C**	T	*KCNJ11*	1.15 (1.05–1.25)	1.3×10^{-3}	–	–	–	–	1.15 (1.09–1.21)	1.0×10^{-7}	1.11 (1.02–1.20)	0.014	1.14 (1.10–1.19)	5.0×10^{-11}
rs1801282	3	12368125	**C**	G	*PPARG*	1.23 (1.09–1.41)	1.3×10^{-3}	–	–	–	–	1.09 (1.01–1.16)	0.019	1.20 (1.07–1.33)	1.4×10^{-3}	1.14 (1.08–1.20)	1.7×10^{-6}

$P < 10^{-5}$) help to limit false discovery, but many genuine susceptibility variants will fail to reach them. We initiated a second wave of replication based around SNPs for which the WTCCC scan generated more modest evidence for association (Cochran-Armitage $P \sim 10^{-2}$ to 10^{-5}). We prioritized the 5367 SNPs in this range using additional criteria: (i) evidence of association in DGI and FUSION (*6*, *7*); (ii) presence of multiple, independent ($r^2 < 0.4$) associations within the same locus; and (iii) biological candidacy (*8*, *18*).

Analysis of the 56 SNPs, representing 49 putative signals, selected for this "second wave" of replication (table S4) yielded two further regions implicated in T2D susceptibility. A cluster of SNPs on chromosome 9 (represented by rs10811661) generated a promising signal in all three scans. Replication was observed in UK samples [rs10811661: OR = 1.18 (CI, 1.08–1.28), $P = 1.7 \times 10^{-4}$), as well as DGI ($P = 2.2 \times 10^{-5}$) and FUSION follow-up studies (rs2383208, $P = 9.7 \times 10^{-3}$). A second signal from the WTCCC scan located ~100 kb 5′ [rs564398, OR = 1.16 (CI, 1.07–1.27), $P = 3.2 \times 10^{-4}$], was weakly supported in the FUSION scan but not the DGI scan (Table 1 and table S3), and was replicated in the U.K. RS samples [OR = 1.12 (CI, 1.05–1.19), $P = 8.6 \times 10^{-4}$] (Table 1 and table S3).

These two association signals are separated by a recombination hotspot (D′ between rs10811661 and rs564398 is 0.057, $r^2 < 0.001$) (Fig. 2). Across all studies, the combined evidence for association is stronger for the 3′ ($P \sim 7.8 \times 10^{-15}$) than for the 5′ ($P \sim 1.2 \times 10^{-7}$) peak (Table 1). The 3′ signal maps to sequence with no characterized genes, whereas the recombination interval enclosing the 5′ signal includes the full coding sequences of *CDKN2B* and *CDKN2A* (encoding $p15^{INK4b}$ and $p16^{INK4a}$, respectively). *CDKN2A* is a known tumor suppressor and its product, $p16^{INK4a}$, inhibits CDK4 (cyclin-dependent kinase 4), a powerful regulator of pancreatic beta cell replication (*19*–*21*). Overexpression of *Cdkn2a* leads to decreased islet proliferation in aging mice (*22*). *Cdkn2b* overexpression is also causally related to islet hypoplasia and diabetes in murine models (*23*). Both *CDKN2B* and *CDKN2A* display high levels of expression in pancreatic islets and pituitary (fig. S2).

A fifth replicated association lies within the *IGF2BP2* gene on chromosome 3. We observed some evidence of association for SNPs in this region in the WTCCC scan (*5*) [e.g., rs4402960: OR = 1.15 (CI, 1.05–1.25), $P = 1.7 \times 10^{-3}$]. Consistent associations in the DGI and FUSION scans (*6*, *7*) and the biological candidacy of the gene [a known regulator of insulin-like growth factor 2 (IGF2) translation] prompted replication. We obtained only modest evidence for replication at rs4402960 [OR = 1.09 (CI, 1.01–1.16), $P = 0.018$] (Table 1 and table S4), but combined evidence across all studies ($P \sim 8.6 \times 10^{-16}$) establishes this as a genuine T2D signal (Table 1 and table S3). The associated SNPs map to a 57-kb region spanning the promoter and first 2 exons of *IGF2BP2* (fig. S4).

Most of the remaining 50 "second-wave" SNPs can be discounted as susceptibility variants based on their failure to replicate (table S4), although some merit further consideration. One such example is rs9369425, located 57-kb downstream of the *VEGFA* (vascular endothelial growth factor A) gene on chromosome 6 (fig. S5). Evidence for association in the WTCCC scan [OR = 1.16 (CI, 1.06–1.27), $P = 8.6 \times 10^{-4}$] is supported by nominal replication in U.K. samples [OR = 1.08 (CI, 1.01–1.15), $P = 0.03$] and by DGI scan results [1.17 (1.04–1.32), $P = 4.4 \times 10^{-3}$]. Although no signal is apparent in the FUSION study, this does not allow us to reject the association. For 80% power to detect an OR of 1.11 ($\alpha = 0.05$), more than 3000 case-control pairs are needed.

In the French genome-wide scan (*14*), variants in both the *HHEX* and *SLC30A8* genes were implicated in T2D susceptibility. Because the associated SNPs in *SLC30A8* are poorly captured on the Affymetrix chip ($r^2 < 0.01$), the WTCCC scan was not informative for this locus. However, we genotyped rs13266634 independently and obtained replication of the finding [risk allele OR = 1.12 (CI, 1.05–1.18), $P = 7.0 \times 10^{-5}$ in all UK data] and across all three studies ($P \sim 5.3 \times 10^{-8}$) (Table 1 and table S4).

The present analysis has contributed to identification of several confirmed T2D susceptibility loci. One of these (*FTO*) exerts its primary effect on T2D risk through an impact on adiposity (*9*): None of the other signals was attenuated by adjustment for BMI or waist circumference (tables S5 to S7). One of the remaining four loci (*HHEX/IDE*) represents a strong replication of findings recently reported (*14*). The other three loci (near *CDKAL1*, *IGF2BP2*, and *CDKN2A*), all showing extensive replication across the three studies, represent previously unknown T2D susceptibility loci.

Across the four T2D scans completed (*5*–*7*, *14*), *TCF7L2* clearly emerges as the largest association signal. On current evidence, all other confirmed loci display more modest effect sizes (between 1.10 and 1.25 per allele). Extensive resequencing and fine-mapping will be required to define the full spectrum of etiological variation at each locus, and these may yet identify variants with greater impact. Our findings offer clear lessons for the design of future studies. Robust identification of variants with such effect sizes is only feasible with large-scale sample sets (13,965 individuals were typed in the present study). Further, the exchange of data between groups (providing data on up to 32,554 samples) was key to the rapid and unequivocal identification of the signals we report.

As a result of the four GWA studies reported to date (*5*–*7*, *14*), the number of genuine, replicated T2D susceptibility signals has climbed from three to nine (adding *HHEX/IDE*, *SLC30A8*, *CDKAL1*, *CDKN2A*, *IGF2BP2*, and *FTO*). However, these loci explain only a small proportion of the observed familiality (the sibling relative risk, λ_s, attributable to all loci in the U.K. samples, is only ~1.07). We expect additional loci to be revealed by further rounds of replication initiated by more systematic meta-analysis of these and other scans. Our study provides an important validation of the genome-wide indirect association mapping approach and a demonstration of the value of aggressive data-sharing efforts. It also generates insights into T2D pathogenesis, emphasizing the likely importance of pathways involved in pancreatic beta cell development, regeneration, and function. In-depth physiological and functional studies are now needed to establish the precise mechanisms involved.

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Supporting Online Material

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A Genome-Wide Association Study of Type 2 Diabetes in Finns Detects Multiple Susceptibility Variants

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Identifying the genetic variants that increase the risk of type 2 diabetes (T2D) in humans has been a formidable challenge. Adopting a genome-wide association strategy, we genotyped 1161 Finnish T2D cases and 1174 Finnish normal glucose tolerant (NGT) controls with >315,000 single-nucleotide polymorphisms (SNPs) and imputed genotypes for an additional >2 million autosomal SNPs. We carried out association analysis with these SNPs to identify genetic variants that predispose to T2D, compared our T2D association results with the results of two similar studies, and genotyped 80 SNPs in an additional 1215 Finnish T2D cases and 1258 Finnish NGT controls. We identify T2D-associated variants in an intergenic region of chromosome 11p12, contribute to the identification of T2D-associated variants near the genes *IGF2BP2* and *CDKAL1* and the region of *CDKN2A* and *CDKN2B*, and confirm that variants near *TCF7L2*, *SLC30A8*, *HHEX*, *FTO*, *PPARG*, and *KCNJ11* are associated with T2D risk. This brings the number of T2D loci now confidently identified to at least 10.

Type 2 diabetes (T2D) is a disease characterized by insulin resistance and impaired pancreatic beta-cell function that affects >170 million people worldwide (*1*). With first-degree relatives having ~3.5 times as much risk as compared to individuals in the general middle-aged population (*2*), hereditary factors, together with lifestyle and behavioral factors, play an important role in determining T2D risk (*3*). To date, intense efforts to identify genetic risk factors in T2D have met with only limited success. This study, reports from our collaborators (*4*–*6*), and the recently published work of Sladek *et al.* (*7*) describe results of genome-wide association (GWA) studies that further define the genetic architecture of T2D and identify biological pathways involved in T2D pathogenesis.

We genotyped 1161 Finnish T2D cases and 1174 Finnish NGT controls on 317,503 SNPs on the Illumina HumanHap300 BeadChip in stage 1 of a two-stage GWA study of T2D (*8*). These samples are from the Finland–United States Investigation of Non-Insulin–Dependent Diabetes Mellitus Genetics (FUSION) (*9*, *10*) and Finrisk 2002 (*11*) studies (tables S1 and S2A). Among the 317,503 GWA SNPs, 315,635 had ≥10 copies of the less common allele [minor allele frequency (MAF) > 0.002] and passed quality-control criteria (*8*). We tested these 315,635 SNPs for association with T2D using a model that is additive on the log-odds scale (Table 1 and tables S3 and S4) (*8*). We observed a modest excess (41 observed versus 31.6 expected; $P = 0.19$) of SNPs with P values $< 10^{-4}$ (fig. S1). These results argue against the existence of multiple common SNPs with a large impact on T2D disease risk but are consistent with the presence of multiple common SNPs that each confer modest risk. The results also suggest that the matching of cases and controls by birth province, sex, and age (*8*) has been successful; in support of this conclusion, the genomic control (*12*) correction value is 1.026.

Analysis of our Illumina HumanHap300 data allowed us to query much of the known SNP variation in the genome. To increase this proportion, we developed an imputation method (*8*, *13*) that uses genotype data and linkage disequilibrium (LD) information from the HapMap Centre d'Etude du Polymorphisme Humain (Utah residents with ancestry from northern and

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Replication of Genome-Wide Association Signals in UK Samples Reveals Risk Loci for Type 2 Diabetes

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