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Large-Scale Gene-Centric Meta-Analysis across 39 Studies Identifies Type 2 Diabetes Loci

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To identify genetic factors contributing to type 2 diabetes (T2D), we performed large-scale meta-analyses by using a custom ~50,000 SNP genotyping array (the ITMAT-Broad-CARE array) with ~2000 candidate genes in 39 multiethnic population-based studies, case-control studies, and clinical trials totaling 17,418 cases and 70,298 controls. First, meta-analysis of 25 studies comprising 14,073 cases and 57,489 controls of European descent confirmed eight established T2D loci at genome-wide significance. In silico follow-up analysis of putative association signals found in independent genome-wide association studies (including 8,130 cases and 38,987 controls) performed by the DIAGRAM consortium identified a T2D locus at genome-wide significance (*GATAD2A/CILP2/PBX4*; $p = 5.7 \times 10^{-9}$) and two loci exceeding study-wide significance (*SREBF1*, and *TH/INS*; $p < 2.4 \times 10^{-6}$). Second, meta-analyses of 1,986 cases and 7,695 controls from eight African-American studies identified study-wide-significant ($p = 2.4 \times 10^{-7}$) variants in *HMGA2* and replicated variants in *TCF7L2* ($p = 5.1 \times 10^{-15}$). Third, conditional analysis revealed multiple known and novel independent signals within five T2D-associated genes in samples of European ancestry and within *HMGA2* in African-American samples. Fourth, a multiethnic meta-analysis of all 39 studies identified T2D-associated variants in *BCL2* ($p = 2.1 \times 10^{-8}$). Finally, a composite genetic score of SNPs from new and established T2D signals was significantly associated with increased risk of diabetes in African-American, Hispanic, and Asian populations. In summary, large-scale meta-analysis involving a dense gene-centric approach has uncovered additional loci and variants that contribute to T2D risk and suggests substantial overlap of T2D association signals across multiple ethnic groups.

Introduction

Type 2 Diabetes (T2D [MIM 125853]) is a complex disease caused by multiple genetic and environmental factors; heritability is estimated at 22%–73% from twin and family studies.^{1–5} The age-adjusted prevalence of T2D in adults has recently been estimated at 7.6% in European Americans, 14.9% in non-Hispanic African Americans, 4.3%–8.2% in Asian Americans, and 10.9%–15.6% in Hispanics.^{6–9} Researchers have identified more than 40 T2D-associated genetic loci, but these loci have been revealed primarily on the basis of studies of individuals of European ancestry. Candidate-gene association studies discovered association between T2D and missense variants in *PPARG* (MIM 601487) and *KCNJ11* (MIM 600937), which are targets for antidiabetic medications, and implicated common genetic variants responsible for Mendelian forms of diabetes in T2D (e.g., such variants include those in the Wolfram-syndrome-associated locus *WFS1* [MIM 606201], those in *HNF1A* [MIM 142410] and *HNF4A* [MIM 600281], and those in genes involved in maturity-onset diabetes of the young [MODY (MIM 125851)]^{10–15}). Association testing near a linkage peak identified common variants in *TCF7L2* (MIM 602228), which remains the strongest signal for T2D and replicates robustly across many,¹⁶ but not all, ethnic groups.¹⁷ Early genome-wide association studies (GWASs) for T2D^{18–22} and fasting glucose²³ successfully identified multiple loci. Recent meta-analyses of GWASs of T2D²⁴ and glycemic quantitative traits²⁵ have dramatically increased the number of genome-wide-significant T2D-associated loci in European populations; most of these variants act through defects in beta-cell function rather than insulin action. Together, variants known to be associated with T2D explain ~10% of the genetic variance,^{24,26} indicating that additional loci and independent signals in established loci are likely to contribute to disease risk.

Genetic contributors to T2D are less well understood in non-European populations. One novel locus (*KCNQ1* [MIM 607542]) was identified on the basis of a GWAS in a Japanese population^{27,28} and has subsequently been shown to harbor independent alleles in individuals of European descent.²⁴ More recently, GWASs in

Chinese,^{29,30} Japanese,³¹ and South Asian populations³² describe additional T2D loci surpassing genome-wide significance. To date, T2D GWASs in African-Americans have been underpowered to detect novel loci.³³

An important first step toward understanding genetic risk across populations is to establish whether known T2D association signals span ethnicities or are population specific. Consistent association of T2D risk variants discovered in Europeans was reported in a multiethnic case-control study of five US populations,³⁴ in studies of Chinese,³⁰ Japanese,³¹ Hispanic³⁵ and South Asian³² populations, and in a study focusing on fasting glucose in an African-American³⁶ population, despite possible differences in linkage disequilibrium (LD) between marker and causal variants in each population. Indeed, multiethnic differences in regional LD help with refinement of association signals and can distinguish causal variants from correlated markers.^{33,37} Furthermore, independent association signals in the same gene (for example, *KCNQ1*) in different ethnicities could be useful for pinpointing genes that harbor causal mutations. Recent power analyses suggest that large-scale multiethnic association studies might have greater statistical power to detect causal alleles because random genetic drift can elevate global risk variants to a higher allele frequency in different populations.³⁸

The 50K SNP Human CVD beadchip, or ITMAT-Broad-CARE (IBC) array, captures genetic diversity across more than 2,000 candidate gene regions related to cardiovascular, inflammatory, and metabolic phenotypes, and a large portion of loci are captured with marker density equal to or greater than that found by GWAS.³⁹ SNPs were selected on the basis of the International HapMap Consortium and publically available resequencing data such as those from the SeattleSNPs and National Institute of Environmental Health Sciences (NIEHS) SNPs consortia. The focus was on the inclusion of rare variants and variants with a high likelihood of functionality. More than 5,000 SNPs from 49 candidate genes (Table S1, available online) were specifically selected on the basis of prior evidence of a role in Mendelian forms of diabetes,⁴⁰ diabetes pathophysiology (including insulin signaling, endocrine pathways, and energy metabolism),⁴¹ linkage studies⁴² and meta-analyses of T2D GWASs.^{18–22} GWAS efforts have

identified additional loci since the design of this array; therefore, of the currently documented T2D loci, 21 candidate genes from eighteen loci and index SNPs from nine additional T2D loci were included on the array. SNP association for this array has been reported for a range of phenotypes, including those involving coronary artery disease,^{43,44} lipid traits,⁴⁵ blood pressure,^{46,47} cardiomyopathy,⁴⁸ blood traits^{49,50} and height.⁵¹

In this study we set out to discover novel T2D loci and attempted to replicate, fine map, and detect independent signals at known loci by combining T2D association results across 39 studies genotyped on the IBC array. We performed meta-analysis in individuals of European ancestry (14,073 cases, 57,489 controls), African-American ancestry (1,986 cases, 7,695 controls), Hispanic ancestry (592 cases, 1,410 controls), and Asian ancestry (767 cases, 3704 controls). Using conditional analyses, we sought to identify additional independent signals within associated loci. Finally, we assessed the concordance of direction of effect of new and established loci and a composite risk score of known loci across ethnicities.

Subjects and Methods

T2D Case and Control Definitions and Participating Studies

For the IBC meta-analyses performed here, T2D cases were defined on the basis of one of the six following criteria: (1) the American Diabetes Association criteria;⁵² (2) fasting (8 hr or longer fast) glucose ≥ 126 mg/dl (≥ 7 mmol/liter); (3) 2 hr glucose ≥ 200 mg/dl (≥ 11.1 mmol/liter) during an oral glucose tolerance test (OGTT); (4) use of diabetes medications; (5) nonfasting plasma glucose > 200 mg/dl, or (6) physician report or self-report of physician-diagnosed diabetes. We selected cases for an age at diagnosis or age at exam ≥ 25 years in order to minimize the inclusion of cases with type 1 diabetes (T1D [MIM 222100]). Glutamic acid decarboxylase (GAD) antibody status was not available in any IBC cohorts, and so we could not definitively exclude subjects with T1D or latent autoimmune diabetes of adults (LADA). Controls within each study were individuals who, on the basis of the criteria described above, were not classified as T2D cases in an exam when they were ≥ 25 years of age.

Clinical and genotype quality-control characteristics from the 39 datasets included in the IBC chip meta-analysis (these datasets consisted of population-based cohorts, collections of cases and controls for metabolic and cardiovascular phenotypes, and individuals collected for clinical trials) are described in Table S2.

All participating studies were required to obtain informed consent for DNA analysis and to have received approval from local institutional review boards. The individuals of European ancestry sampled in the primary analysis were independent from the subjects included in the eight component studies of the previously reported DIAGRAM GWAS meta-analysis used for in silico replication.²⁴ GAD antibody status was available for subjects from four component GWASs of the DIAGRAM consortium, and T2D association results for each component DIAGRAM study were obtained for SNPs rs9273363 (*HLA-DQB1* [MIM 604305]) and rs10770141 (*TH/INS* region [MIMs 191290 and 176730]) from the DIAGRAM investigators.

Genotyping and Quality Control

Genotyping in each component study of the IBC meta-analysis was performed with the IBC array.³⁹ SNPs were clustered into genotypes with the Illumina Beadstudio software and subjected to quality-control filters at the sample and SNP levels separately within each cohort. Samples were excluded for individual call rates $< 90\%$, gender mismatch, and duplicate discordance. SNPs were removed for call rates $< 95\%$ or Hardy-Weinberg equilibrium $p < 10^{-7}$ in controls from each cohort (regardless of ethnicity). Because of the low-frequency SNPs included in the design and the aim to capture low-frequency variants of large effect across the large dataset, we filtered only on minor allele frequency (MAF) < 0.005 .

Statistical Analyses

Evaluation of Population Stratification

For the primary meta-analysis, only individuals of European ancestry were included. Self-reported ethnicity was verified by multidimensional scaling (MDS) analysis of identity-by-state distances as implemented in PLINK; HapMap panels were included as reference standards. After SNPs in LD ($r^2 > 0.3$) were pruned out, Eigenstrat was used for computing principal components on the subset of nonexcluded individuals for use as covariates in the regression analyses.^{53,54}

Association Testing

We performed T2D association analysis in each study by using an additive genetic model. Our primary association analysis included adjustment for age, sex, body-mass index (BMI), study site(s), and principal components (PCs) if population structure was evident. The genomic control inflation factor, λ , was calculated in each case-control study and used for within-study correction before meta-analysis. λ ranged from 1.0 to 1.077. As the Look AHEAD study^{55,56} was a case-only study, we merged this dataset with 4,124 randomly selected ARIC controls of European ancestry for association analysis. After performing stringent quality control, we found limited population structure between the two datasets and a λ of 1.04. ARIC individuals used for the Look AHEAD (cases)/ARIC (controls) sample were not included in the ARIC IBC association analysis reported here (1,278 ARIC cases and 2,600 independent ARIC controls). Notably, Look AHEAD participants were obese (with an average BMI of 36.0 ± 5.9 kg/m²), and ARIC controls selected for matching were not (average BMI of 27.7 ± 5.2 kg/m²). Despite BMI adjustment, this discrepancy could lead to T2D association signals arising from SNP associations to BMI.

Meta-analyses within each ethnic group were performed by two independent analysts who used a fixed-effect inverse-variance approach in two different software packages: MANTEL and METAL.³³ After association tests in each ethnicity, a multiethnic meta-analysis that included all available participants was performed. Additionally, the direction of effect of lead SNPs from previously identified loci was evaluated for consistency in African-Americans, Hispanics, and Asians.

Previous studies using the IBC array have used different significance thresholds, from $p < 1 \times 10^{-5}$ to $p < 1 \times 10^{-6}$.^{43, 45} To calculate an appropriate significance threshold, we used data from the Candidate Gene Association Resource (CARE) IBC array studies⁵⁷ and determined that after LD was accounted for, the effective number of independent tests was $\sim 26,500$ for African Americans and $\sim 20,500$ for Europeans. This produces an experimental or study-wide statistical threshold of $p = 1.9 \times 10^{-6}$ and $p = 2.4 \times 10^{-6}$, respectively, if a false-positive rate of 5% is to be

maintained. Consistent with the hypothesis-driven candidate gene approach taken here, we have adopted these “array-wide” or study-wide statistical thresholds for this study, but we also highlight loci significantly associated at a more conventional genome-wide-significant threshold of $p < 5.0 \times 10^{-8}$.

For confirmation of signals previously associated with T2D, we selected the exact SNP from the most recent discovery study or meta-analysis when possible. If the SNP was not present on the array, we selected from the IBC array a SNP that was in highest linkage disequilibrium with the previously identified SNP in the HapMap CEU (Utah residents with northern and Western European ancestry from the CEPH collection) population (this SNP was identified with the online tool SNAP). Selected SNPs and r^2 to previously associated SNPs are shown in Table S1.

Conditional Analyses

Forty-six loci harboring nominally significant evidence for association ($p < 1.0 \times 10^{-4}$) were examined for additional signals via conditional analyses in PLINK.⁵⁸ A term was added to the regression model so that the lead SNP was included as a covariate, and SNPs within the same candidate gene, or ± 200 kb if the candidate gene region was <200 kb, were evaluated for significance. Conditional analysis was performed in fifteen European and eight African-American cohorts with individual-level genotype data. We applied a locus-specific Bonferroni correction (i.e., correction for SNPs tested within the same candidate gene or within 200 kb if the candidate gene region was <200 kb) to determine the significance of independent signals within candidate genes genotyped at each locus. Table S1 shows the number of SNPs (and therefore tests) per locus on which the locus-wide significance level was based.

Genetic-Risk-Score Analyses

In eight African-American, Asian, and Hispanic cohorts from the CARE study, we generated a genetic-risk score of 27 T2D-associated SNPs (26 previously established genome-wide-significant T2D-associated SNPs and the index SNP from the *GATAD2A* signal from this study) weighted by the log of the OR from meta-analyses of GWASs^{24,25} as described previously.⁵⁹ We evaluated the contribution of the weighted genetic risk score to T2D in logistic regression models adjusting for age, gender, BMI, and ten principal components and compared the relative ORs across quartiles of risk.

Results

Meta-Analysis of Samples of European Ancestry

We performed association testing for T2D status (tests included 14,073 cases and 57,489 controls) and adjusted for age, gender, BMI, and three or more PCs in 25 European IBC studies. After a fixed-effects, inverse-variance meta-analysis, independent SNPs at *HLA-DQB1*, *SREBF1* (MIM 184756), *GATAD2A/CILP2* (MIM 612419)/*PBX4* (MIM 608127), *BCL2* (MIM 151430), and 16 previously described loci were significantly associated with T2D at study-wide significance ($p < 2.4 \times 10^{-6}$), and SNPs at eight known loci surpassed the traditional genome-wide-significance threshold ($p < 5.0 \times 10^{-8}$; Tables 1 and 2; Figures S1A and S1B). Of the study-wide significant loci, SNPs correlated to the most significant *SREBF1* polymorphism ($r^2 > 0.85$ in HapMap CEU) have been reported previously in candidate-gene analyses^{60,61} but not in large-scale genomic studies with robust replication. Our sample-selection and study-

design strategies are validated by study-wide-significant independent replication of 14 out of 29 previously reported T2D-associated loci present on the IBC chip (Table 2) and nominal association of 23/29 loci with a consistent direction of effect for all signals. For five T2D association signals tagged by variants on the IBC array (these signals were in or near *RBMS1* [MIM 602310], *CENTD2* [MIM 606646], *ZFAND6* [MIM 610183], *HMGA2* [MIM 600698], or *HNF1A*), overlapping samples from four component studies (ARIC, CCCS, FHS, and KORA) were included in the initial report,²⁴ and therefore our results are not independent.

In order to confirm putative novel signals, we carried out in silico follow-up analyses of 25 SNPs from previously undescribed T2D-associated signals ($p < 1.0 \times 10^{-4}$) in a meta-analysis of eight GWASs ($n = 8,130$ cases and 38,987 controls of European ancestry) from the DIAGRAM consortium.²⁴ Combined meta-analyses of the discovery and replication studies led to genome-wide-significant signals at the *GATAD2A/CILP2/PBX4* ($p = 5.7 \times 10^{-9}$) and *HLA-DQB1* ($p = 1.1 \times 10^{-8}$) loci; the signal at *SREBF1* remained study-wide significant, and a signal at *TH/INS* became study-wide significant (Table 1, Figures 1A–1D). Furthermore, 12/18 additional SNPs displayed a direction of effect consistent with our discovery dataset, suggesting that additional loci might have weaker effects that are undetectable as a result of limited statistical power (Table S3). Lead or correlated SNPs for three signals with $p < 10^{-5}$ in the IBC meta-analysis at the *BCL2*, *CDKN1B* (MIM 600778), and *SLC39A4* (MIM 607059) loci were not included in the DIAGRAM meta-analysis (Table S3), and these signals, as well as our study-wide-significant findings, will need independent follow-up in future studies of European ancestry.

The *HLA-DQB1* allele has previously been demonstrated to exhibit a strong association with type 1 diabetes (odds ratio [OR] > 5.4). To determine whether the association signal observed at this locus was driven by cases with LADA, we examined association of this SNP in DIAGRAM component studies with and without exclusion of GAD-antibody-positive cases. We observed a trend toward more significant association of the SNP in meta-analysis of studies including LADA than in the study set that excluded LADA (Table S4), suggesting this signal might indeed stem from a subset of cases with autoimmune diabetes misclassified as T2D; however, this difference was not statistically significant ($P_{\text{het}} = 0.51$). To explore whether rs9273363 in *HLA-DQB1* in fact represents a T1D signal, we imputed classical HLA alleles in 10,636 cases and 38,063 controls from our IBC dataset by using a reference set of 2,767 European individuals with four-digit genotype data for *HLA-A* (MIM 142800), *HLA-B* (MIM 142830), *HLA-C* (MIM 142840), *HLA-DQA1* (MIM 146880), *HLA-DQB1*, *HLA-DRB1* (MIM 142857), *HLA-DPA1* (MIM 142880), and *HLA-DPB1* (MIM 142858).⁶² After imputation, we tested imputed classical HLA alleles for association with T2D by using logistic regression including age, sex, BMI, study site, and three PCs as

Table 1. Loci Associated with T2D in Individuals of European Ancestry

Chr	NCBI 36 Position	Candidate Gene ^d	SNP	RA	RAF IBC	European-Ancestry IBC Meta-Analysis ^a			DIAGRAM Meta-Analysis ^b		Combined European Ancestry Meta-Analysis ^c		
						OR (95% CI)	p	% I ²	OR (95% CI)	p	OR (95% CI)	p	Percent I ²
SNPs with Study-wide Significance													
19	19471596	<i>GATAD2A</i>	rs3794991	T	0.08	1.14 (1.08–1.20)	8.95×10^{-7}	25	1.11 (1.04–1.17)	1.55×10^{-3}	1.12 (1.08–1.15)	5.70×10^{-9}	22
17	17662182	<i>SREBF1</i>	rs4925115	A	0.38	1.09 (1.05–1.12)	2.04×10^{-7}	0	1.04 (0.99–1.08)	1.01×10^{-1}	1.07 (1.04–1.10)	2.62×10^{-7}	0
11	2150416	<i>TH/INS</i>	rs10770141	A	0.39	1.07 (1.04–1.11)	6.44×10^{-6}	0	1.05 (1.00–1.10)	7.08×10^{-2}	1.07 (1.04–1.10)	1.57×10^{-6}	0
18	58996864	<i>BCL2</i>	rs12454712	T	0.63	1.08 (1.04–1.11)	2.29×10^{-6}	21	-	-	-	-	-
SNPs with Borderline Significance^e													
11	49127350	<i>FOLH1</i>	rs16906158	C	0.09	1.13 (1.07–1.19)	8.75×10^{-6}	32	1.07 (1.00–1.14)	5.17×10^{-2}	1.10 (1.06–1.15)	2.57×10^{-6}	32
3	172217793	<i>SLC2A2</i>	rs11924032	G	0.74	1.08 (1.04–1.12)	1.87×10^{-5}	0	1.05 (1.00–1.10)	3.31×10^{-2}	1.06 (1.04–1.10)	2.60×10^{-6}	0
19	50864118	<i>GIPR</i>	rs11671664	A	0.11	1.12 (1.07–1.18)	2.86×10^{-6}	0	1.06 (0.98–1.14)	1.71×10^{-1}	1.10 (1.06–1.15)	2.61×10^{-6}	0
SNPs with Likely Association to LADA or Autoimmune Diabetes Component^f													
6	32734250	<i>HLA-DQB1</i>	rs9273363	A	0.27	1.10 (1.06–1.14)	7.99×10^{-8}	17	1.06 (1.01–1.10)	1.64×10^{-2}	1.08 (1.05–1.11)	1.10×10^{-8}	19

Abbreviations are as follows: Chr, chromosome; RA, risk allele; RAF, risk-allele frequency; OR, odds ratio; and CI confidence interval.

^a14,073 cases and 57,489 controls.

^b8,130 cases and 38,987 controls.

^c22,203 cases and 94,476 controls.

^dCandidate gene selected for testing on the array.

^eIBC Study-wide significance = $p < 2.4 \times 10^{-6}$.

^fSee Tables S4 and S5.

Table 2. Association Results for Known T2D Loci in Meta-Analysis of IBC Studies of European Ancestry

Chr	Prev. Assoc. SNP	Pos (NCBI 36)	Candidate Gene	Lead SNP on IBC array	r2 to Prev. Assoc. SNP	RA	RAF IBC	OR (95% CI)	p	I ² (%)
1	rs10923931	120,319,482	<i>NOTCH2</i>			T	0.10	1.06 (1.01–1.12)	3.23×10^{-2}	21.0
1		120,239,407	<i>NOTCH2</i>	rs2641348	0.85 (rs10923931)	G	0.11	1.06 (1.01–1.12)	1.95×10^{-2}	16.0
2	rs780094	27,594,741	<i>GCKR</i>	rs780094	0.93 (rs1260326)	C	0.59	1.09 (1.05–1.12)	2.12×10^{-7}	43.0
2	rs7578597	43,586,327	<i>THADA</i>	rs7578597		T	0.90	1.16 (1.10–1.22)	2.91×10^{-7}	34.4
2	rs7593730	160,879,700	<i>RBMS1</i>	rs6718526	0.83 (rs7593730)	C	0.79	1.03 (0.99–1.07)	1.20×10^{-1}	0
3	rs1801282	12,368,125	<i>PPARG</i>			C	0.88	1.11 (1.10–1.16)	2.15×10^{-5}	0
3		12,367,272	<i>PPARG</i>	rs7649970	1 (rs1801282)	C	0.88	1.11 (1.06–1.16)	7.87×10^{-6}	0
3	rs4607103	64,686,944	<i>ADAMTS9</i>			C	0.74	1.05 (1.02–1.10)	4.11×10^{-3}	0
		64,676,186	<i>ADAMTS9</i>	rs9860730	0.69 (rs4607103)	A	0.68	1.05 (1.02–1.09)	1.24×10^{-3}	0
3	rs1470579	187,011,774	<i>IGF2BP2</i>	rs1470579		C	0.32	1.14 (1.10–1.18)	9.19×10^{-16}	8.8
4	rs10010131	6,343,816	<i>WFS1</i>			G	0.60	1.10 (1.01–1.20)	3.37×10^{-2}	76.9
		6,336,616	<i>WFS1</i>	rs4688985	0.58 (rs10010131)	G	0.73	1.10 (1.05–1.14)	2.88×10^{-7}	34.8
6	rs7754840	20,769,229	<i>CDKAL1</i>			C	0.32	1.16 (1.12–1.20)	4.58×10^{-19}	0
		20,794,975	<i>CDKAL1</i>	rs9368222	0.63 (rs7754840)	A	0.27	1.18 (1.14–1.22)	5.37×10^{-21}	0
7	rs10244051	15,030,358	<i>DGKB-TMEM195</i>	rs10244051	1 (rs2191349)	G	0.54	1.04 (0.95–1.14)	4.02×10^{-1}	55.3
7	rs864745	28,147,081	<i>JAZF1</i>	rs864745	0.97 (rs849134)	T	0.50	1.11 (1.08–1.14)	2.22×10^{-9}	31.3
7	rs4607517	44,202,193	<i>GCK</i>			A	0.18	1.10 (0.98–1.23)	1.07×10^{-1}	0
7		44,189,327	<i>GCK</i>	rs1990458	0.18 (rs4607517)	C	0.59	1.08 (1.04–1.11)	1.67×10^{-6}	0
8	rs13266634	118,253,964	<i>SLC30A8</i>	rs13266634		C	0.70	1.11 (1.08–1.15)	2.49×10^{-9}	29.5
9	rs10811661	22,124,094	<i>CDKN2A/B</i>	rs10811661		T	0.82	1.19 (1.14–1.23)	4.83×10^{-16}	0
10	rs12779790	12,368,016	<i>CDC123/CAMK1D</i>	rs12779790		G	0.18	1.07 (0.99–1.15)	7.28×10^{-2}	4.7

Table 2. Continued

Chr	Prev. Assoc. SNP	Pos (NCBI 36)	Candidate Gene	Lead SNP on IBC array	r2 to Prev. Assoc. SNP	RA	RAF IBC	OR (95% CI)	p	I ² (%)
10	rs5015480	94,455,539	<i>HHEX/IDE</i>	rs5015480		C	0.60	1.12 (1.10–1.16)	2.68×10^{-14}	12.3
10	rs7903146	114,748,339	<i>TCF7L2</i>	rs7903146		T	0.30	1.44 (1.40–1.49)	1.21×10^{-109}	27.6
11	rs163184	2,803,645	<i>KCNQ1</i>	rs163184		G	0.48	1.08 (1.05–1.11)	6.08×10^{-7}	0
11	rs2237892	2,796,327	<i>KCNQ1</i>	rs2237892		C	0.94	1.11 (0.92–1.37)	2.61×10^{-1}	0
11	rs231362	2,648,047	<i>KCNQ1</i>	rs231362		G	0.52	1.08 (1.04–1.11)	5.90×10^{-6}	3.8
11	rs5215	17,365,206	<i>KCNJ11</i>	rs5215	0.93 (rs5219)	C	0.37	1.09 (1.06–1.13)	1.65×10^{-8}	15.2
11	rs1552224	72,110,746	<i>CENTD2</i> region	rs613937	0.86 (rs1552224)	A	0.81	1.08 (1.04–1.13)	1.17×10^{-4}	0
11	rs10830963	92,348,358	<i>MTNR1B</i>	rs10830963		G	0.30	1.05 (1.01–1.08)	8.07×10^{-3}	21.0
11	rs2943634	226,776,324	<i>IRS1</i> region	rs2943634	0.82 (rs7578326)	C	0.67	1.09 (1.05–1.12)	4.32×10^{-7}	16.4
12	rs7961581	69,949,369	<i>TSPAN8/LGR5</i>	rs7961581	0.87 (rs4760790)	G	0.71	1.06 (1.01–1.10)	1.57×10^{-2}	0
12		64,569,867	<i>HMG2</i>	rs17179453	0.57 (rs1531343)	C	0.09	1.10 (1.05–1.16)	3.73×10^{-4}	11.9
12	rs7957197	119,945,069	<i>HNF1A</i>	rs12427353	0.88 (rs7957197)	G	0.77	1.07 (1.03–1.12)	4.76×10^{-4}	0
15		78,200,439	<i>ZFAND6</i>	rs2903265	0.71 (rs11634397)	G	0.72	1.01 (0.98–1.05)	4.62×10^{-1}	4.2
16	rs11642841	52,402,988	<i>FTO</i>	rs11642841		A	0.41	1.06 (1.03–1.09)	1.78×10^{-4}	14.8
17	rs4430796	33,172,153	<i>HNF1B</i>	rs4430796	0.54 (rs757210)	G	0.51	1.08 (1.05–1.12)	2.48×10^{-7}	0
X	rs5945326	152,553,116	<i>DUSP9</i>	rs5945326		A	0.77	1.09 (1.03–1.15)	2.53×10^{-3}	0

The study included 14,073 cases and 57,489 controls. Abbreviations are as follows: Chr, chromosome; Prev. assoc., previously reported T2D-associated SNP; Pos, position; RA, risk allele; RAF, risk-allele frequency; OR, odds ratio; and CI, confidence interval.

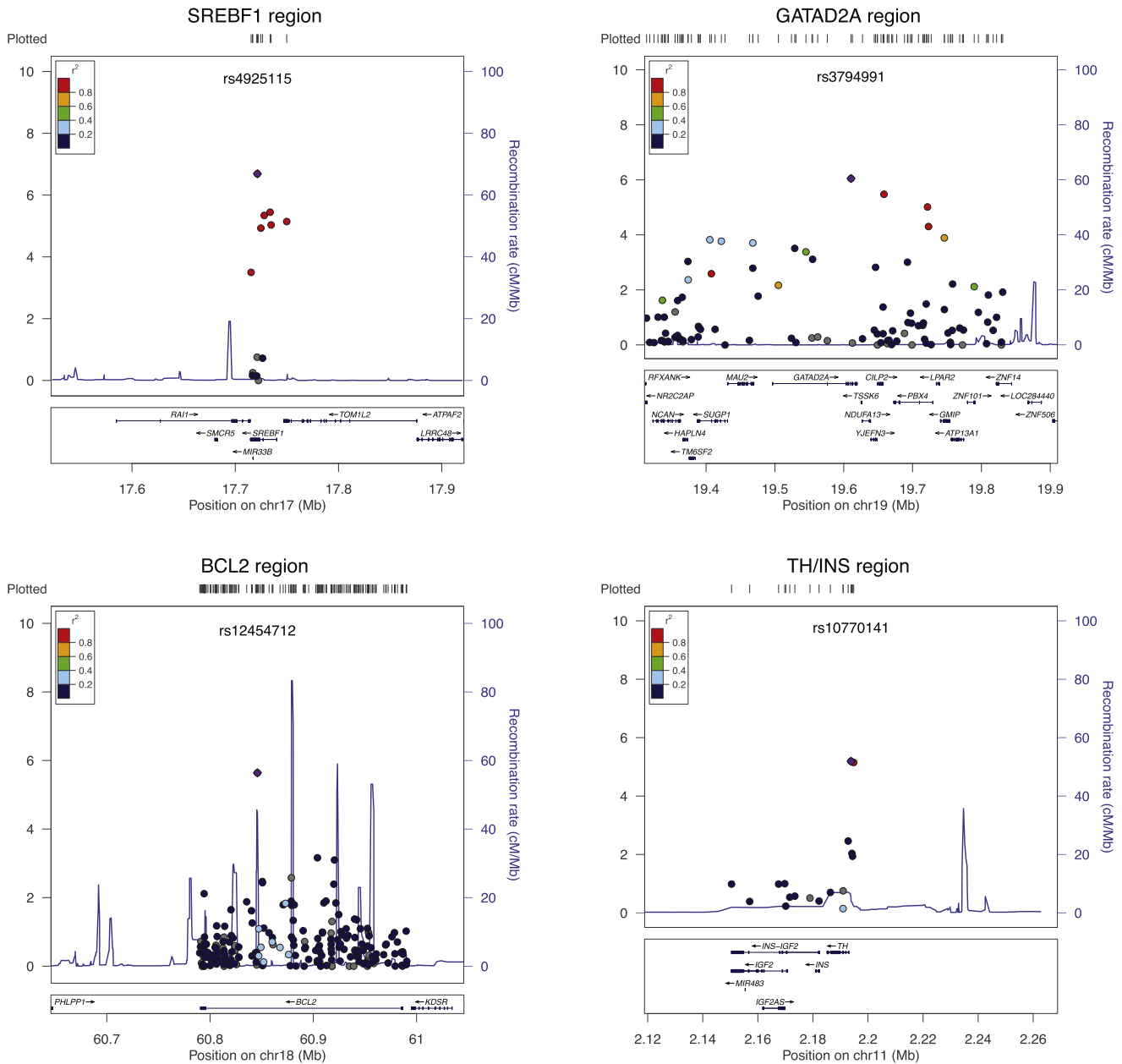


Figure 1. Regional Plots for T2D Loci with Study-Wide-Significant Regions in IBC Meta-Analysis of Data from Individuals with European Ancestry

Loci are shown as the lead SNP with a flanking region depicting the candidate gene and nearby genes included on the array. The purple diamond represents the lead SNP in the IBC meta-analysis, and the dots represent the surrounding SNPs; colors show the LD relationship with the lead SNP on the basis of CEU HapMap II information. $-\log_{10}$ p values for association with T2D are shown for each SNP (left-hand axis). Recombination rates in CEU HapMap II are shown in blue traces (right-hand axis).

covariates. *HLA-DQA1* was identified as the signal that was the most significantly associated with T2D (*HLA-DQA1*03*; $p = 2.8 \times 10^{-7}$) and was closely followed by *HLA-DRB1* (*HLA-DRB1*04*; $p = 3.6 \times 10^{-7}$; Table S5). *HLA-DQB1*, *HLA-DQA1*, and *HLA-DRB1* are major genetic determinants of T1D,^{63–65} suggesting that the observed association at HLA SNPs is an artifact caused by LADA pollution of our cases. We repeated association analysis conditioning on lead SNPs to identify other HLA-region loci that were associated with T2D (both rs9273363 and

*HLA-DQA1*03*), but we found no additional association signals.

Independent Signals at European T2D-Associated Loci

An advantage of our study over a GWAS is the inclusion of rare missense SNPs at candidate loci. Such SNPs can help identify independent T2D signals within genes at known loci. We performed regional conditional-association analyses by adjusting for lead SNPs at 46 signals with $p < 10^{-4}$ in 10,636 cases and 38,063 controls of European

Table 3. Loci with Significant Evidence of Independent T2D Association Signals

Gene	SNP	Chr.	NCBI36 Position	Effect Allele	Freq. IBC	Original Results		Conditional Results		
						OR (95% CI)	p	OR (95% CI)	p	r ² with Lead SNP*
IBC European Ancestry						(14,073 cases and 57,489 controls)		(10,636 cases and 38,063 controls)		
<i>CDKN2A/B</i>	rs10811661	9	22,124,094	C	0.176	0.84 (0.81–0.88)	4.83 × 10 ⁻¹⁶			
	rs10757282	9	22,123,984	C	0.433	1.04 (1.01–1.08)	2.23 × 10 ⁻²	1.14 (1.10–1.18)	2.41 × 10 ⁻¹⁰	0.36
<i>KCNQ1</i>	rs163184	11	2,803,645	G	0.482	1.08 (1.05–1.11)	6.08 × 10 ⁻⁷			
	rs231362	11	2,648,047	A	0.477	0.93 (0.90–0.96)	5.90 × 10 ⁻⁶	0.90 (0.87–0.94)	1.98 × 10 ⁻⁷	0.025
<i>PPARG</i>	rs17036160	3	12,367,272	T	0.121	0.90 (0.86–0.94)	7.87 × 10 ⁻⁶			
	rs1797912	3	12,445,239	A	0.636	1.06 (1.03–1.09)	5.48 × 10 ⁻⁵	1.08 (1.04–1.13)	6.15 × 10 ⁻⁵	0.053
<i>THADA</i>	rs7578597	2	43,586,327	C	0.105	0.86 (0.82–0.91)	2.91 × 10 ⁻⁷			
	rs10200833	2	43,526,820	C	0.342	0.94 (0.91–0.98)	2.63 × 10 ⁻³	0.92 (0.88–0.96)	4.71 × 10 ⁻⁴	0.047
<i>JAZF1</i>	rs864745	7	28,147,081	C	0.502	0.90 (0.88–0.93)	2.22 × 10 ⁻⁹			
	rs12113122	7	28,147,769	G	0.051	1.55 (1.11–2.15)	5.13 × 10 ⁻²	1.42 (1.11–1.62)	1.21 × 10 ⁻²	0.002
IBC African Americans						(1,986 cases and 7,695 controls)		(1,867 cases and 7,580 controls)		
<i>HMG2</i>	rs9668162	12	64,555,049	G	0.222	1.26 (1.15–1.37)	2.41 × 10 ⁻⁷			
	rs1042725	12	64,644,614	T	0.38	1.08 (1.00–1.16)	3.76 × 10 ⁻²	1.14 (1.06–1.24)	0.00299	0.046

ancestry. After Bonferroni correction for SNPs at the candidate gene locus, we found independent novel T2D signals at the *PPARG*, *THADA* (MIM 611800), and *JAZF1* (MIM 606246) loci and confirmed known secondary signals at *CDKN2A* (MIM 600160)/*CDKN2B* (MIM 600431) and *KCNQ1*^{22,24} (Table 3). Additionally, Table S6 shows seven locus-wide-significant signals in loci with primary associations of $p < 2.5 \times 10^{-4}$ in our study; these loci include *GIPR*, which was recently associated with 2 hr glucose levels during an OGTT.⁶⁶

T2D Meta-Analysis in Multiethnic Populations

We next performed meta-analysis across IBC-array T2D-association results independently in eight African-American studies (1,986 cases, 7,695 controls), three Hispanic-Latino studies (592 cases, 1,410 controls), and three Asian studies (767 cases, 3704 controls). Although these analyses were underpowered to detect novel loci at genome-wide significance in these populations, we could evaluate the contribution of known and identified T2D loci to disease risk across ethnicities (Table S7).

In African Americans, study-wide significant association was observed for SNPs within *TCF7L2* (rs7903146 $p = 5.1 \times 10^{-15}$) and within *HMG2* (rs9668162 $p = 2.4 \times$

10^{-7} ; Table S7). *HMG2* encodes a transcriptional regulator of *IGF2BP2* (MIM 608289), a gene known to be associated with T2D, and a T2D-associated signal ~43 kb upstream of *HMG2* was recently described in a European GWAS meta-analysis performed by the DIAGRAM consortium ($r^2 = 0.005$ in CEU, $r^2 = 0.35$ in YRI [Yoruba in Ibadan, Nigeria] to best European SNP;²⁴). Because our array coverage was limited to the *HMG2* region, we cannot confirm whether the African-American signal observed is independent from the previously reported *HMG2* signal in Europeans; however, conditional analysis in African-American studies revealed two locus-wide-significant associations (Table 3).

We further investigated whether the African-American meta-analysis could refine localization of known T2D-associated signals on the basis of differential LD or reveal novel independent signals within genes known to be associated with T2D. Three suggestive missense association signals were identified for evaluation in future case-control association studies. These signals included (1) rs34150427 in *KCNQ1* (V648I/V521I; MAF 0.02; $p = 6 \times 10^{-5}$), which was absent in Europeans; (2) rs1801208 in *WFS1* (R456H; MAF 0.04; $p = 0.001$); and (3) rs16889462 in *SLC30A8* (MIM 611145), a SNP adjacent to known T2D-associated

Table 4. Prediction of Risk of T2D in CARE African-American, Hispanic, and Asian Populations via a Weighted Genetic Score of 27 T2D Variants

	African-American	Hispanics	Asians
Additive Risk per Allele			
N (cases/controls)	1801/7253	297/874	109/529
OR (95% CI)	1.06 (1.04–1.08)	1.07 (1.03–1.12)	1.12 (1.04–1.22)
p	1.07×10^{-10}	0.0021	0.0047
Quartiles of Risk Alleles			
Q1 OR (95% CI)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Q2 OR (95% CI)	1.13 (0.96–1.33)	1.06 (0.69–1.61)	1.77 (0.88–3.57)
p	0.14	0.802	0.114
Q3 OR (95% CI)	1.45 (1.24–1.70)	1.28 (0.85–1.94)	1.64 (0.81–3.33)
p	5.01×10^{-6}	0.24	0.17
Q4 OR (95% CI)	1.53 (1.31–1.80)	1.69 (1.12–2.57)	2.63 (1.37–5.05)
p	1.90×10^{-7}	0.013	0.0035

The 27 T2D variants on the IBC chip include 26 T2D-associated variants in Table S1 and the lead SNP in the *GATAD2A* region. $p = 0.34$ for heterogeneity of allelic effects across ethnic groups.

SNP rs13266634, which alters codon R324 (MAF = 0.10; $p = 0.017$) and was rare in Europeans (MAF = 0.02, $p = 0.28$; Figures S2A–S2C).

In a multiethnic meta-analysis of all available IBC case-control samples, 14 loci retained study-wide significance (Table S7), and a variant in *BCL2* attained genome-wide significance (rs12454712T OR = 1.09 [95% confidence interval (CI): 1.05–1.11], $p = 2.1 \times 10^{-8}$). Concordance in direction of effect was observed for 27 of 40 T2D association signals between Europeans and African Americans ($p = 0.011$). Thirty-two SNPs were concordant in direction of effect between Europeans and Hispanics ($p = 7.0 \times 10^{-5}$), and 27 SNPs were concordant between Europeans and Asians ($p = 0.011$). A total of 17 out of 40 SNPs were concordant across all four ethnic groups. A combined genetic risk score, comprising 26 previously described, robustly T2D-associated variants (listed in Table S1) and the genome-wide-significant *GATAD2A*-region signal discovered in this study, demonstrated a significant per-allele risk effect in African-American (OR = 1.06 [95% CI: 1.04–1.08]; $p < 10^{-10}$), Hispanic (OR = 1.07 [95% CI: 1.03–1.12]; $p < 10^{-3}$), and Asian cohorts (OR = 1.12 [95% CI: 1.04–1.22]; $p < 10^{-3}$) from the CARE study (Table 4), suggesting overlap of causal T2D risk alleles across multiple ethnic groups.

Discussion

This study reports a large meta-analysis of T2D-candidate-gene association studies and has identified three additional

diabetes-associated loci, verified known T2D-associated loci, and uncovered multiple independent T2D association signals, demonstrating the power of large collaborative approaches to uncover genetic insights in T2D. Furthermore, we have evaluated the impact of established T2D risk variants on risk of T2D in multiethnic populations.

Samples were assembled primarily through population-based studies and clinical trials; only one study (Look AHEAD) solely recruited T2D cases. As a validation of samples included in this study, 22 of 25 studies of European ancestry showed the expected association of *TCF7L2* SNPs at $p < 0.05$ in the expected direction (Table S8), and 25 of 27 known T2D index SNPs or close proxies were replicated with $p < 0.05$ as described. A particular strength of our study as compared to other large-scale meta-analyses of T2D is that all participating studies performed association analyses adjusted for sex, age, and BMI, reducing confounding effects.

We identified a novel diabetes-associated locus at *GATAD2A/CILP2/PBX4*, included on the IBC array because it was previously described as being associated with lipid levels.³⁹ *GATAD2A* rs3794991 is in strong LD ($r^2 > 0.90$ in HapMap CEU) with rs16996148 (near *CILP2/PBX4*), previously associated with low-density lipoprotein (LDL) cholesterol and triglycerides (TGs) in meta-analysis of GWAS⁶⁷ and in previous IBC studies of TG levels.⁴⁵ Interestingly, the LDL and TG-lowering allele is associated with increased risk of T2D, reminiscent of the contrasting effects on T2D and triglyceride levels of the pleiotropic missense P446L SNP in *GCKR*.⁶⁸ *GATAD2A* encodes the GATA zinc finger domain containing 2A, a transcriptional repressor that interacts with the methyl-CpG-binding domain proteins MBD2 (MIM 603547) and MBD3 (MIM 603573). Methyl-CpG-binding domain proteins mediate functional responses of methylated DNA. *PBX4* encodes a homeodomain protein with similarity to a transcription factor involved in translocations in pre-B cell leukemias, and *CILP2* encodes cartilage intermediate layer protein 2. Further studies are needed to establish the genetic variants that contribute to diabetes and lipid traits and to establish the causal mechanisms at this locus.

T2D-associated SNPs at the second genome-wide significant locus, the *HLA-DQB1* region, have previously been strongly associated with type 1 diabetes (T1D) as one of four independent signals from the HLA region.⁶⁵ This signal most likely represents association with LADA in both the IBC array and DIAGRAM T2D datasets; among most T2D studies, approximately 10% of “cases” are actually misdiagnosed individuals with LADA.⁶⁹ An alternative hypothesis is that T1D risk alleles confer a much weaker risk to T2D.⁷⁰ In this study, we show that the association of HLA SNPs with T2D is most likely an artifact caused by the inclusion of misdiagnosed individuals with LADA in our study, as indicated both by the comparison of DIAGRAM component studies with and without LADA cases and fine mapping of the major signal in the HLA

region. If we assume an OR of 5.49 for the HLA signal in the LADA cases,⁷¹ we estimate the percentage of LADA cases in our total cases set to be 7.6%, consistent with previous estimates.⁶⁹

A second T1D risk allele (rs10770141, located in the promoter region of tyrosine hydroxylase [*TH*] and 11 kb upstream of the insulin (*INS*) gene) was study-wide significant, but interestingly, this T1D risk allele was protective for T2D. Although located close to the insulin gene, this SNP regulates expression of *TH*; the T2D risk allele increases expression, and the T1D risk allele lowers expression.^{72,73} The signal is not correlated with a minisatellite upstream of the insulin gene; this minisatellite has previously been inconsistently associated with risk of T2D.^{74,75} Replication in independent cohorts will be important for the validation of this finding, and functional studies will be required to establish whether causal variants at this locus indeed act antagonistically to contribute to type 1 and type 2 diabetes. No significant association with T2D was found for other SNPs that had genome-wide-significant associations with T1D (Table S9).

The fourth signal resides in *SREBF1*, which encodes the transcription factors sterol-regulatory-element-binding protein (SREBP)-1a and -1c. Whereas SREBP1a is ubiquitously expressed, SREBP1c is particularly expressed in insulin-sensitive tissues such as liver and adipose. SREBP1a and SREBP1c control lipid synthesis and glucose metabolism by regulating the expression of key genes involved in glucose, fatty acid, and triglyceride metabolism.^{76,77} Variants in *SREBF1* have previously been shown to be associated with T2D in several candidate-gene studies.^{60,61,78–80} All reported associated variants are in substantial LD with our most significantly associated SNP, rs4925115 (1000 Genomes Pilot 1: $r^2 = 0.81–0.89$). However, thus far GWASs have not detected *SREBF1* as a T2D locus, perhaps because most GWASs did not systematically adjust for the confounding factors of sex, age and BMI, and these adjustments were demonstrated to be essential for detection of this association in a previous study.⁶⁰ Specifically, in the DIAGRAM meta-analysis, most component studies did not adjust for sex, age, and BMI, providing a likely explanation as to why the *SREBF1* signal was not strongly replicated (Table 1).

T2D association signals that were close to study-wide significance include compelling candidates previously confirmed as associated with glycemic diabetes-related traits; such candidates include *MADD* (MIM 603584) near *FOLH1* (MIM 600934),²⁵ the glucose transporter 2 isoform *SLC2A2* (MIM 138160),²⁵ and gastric inhibitory polypeptide receptor *GIPR* (MIM 137241).⁶⁶ These suggestive findings are consistent with the hypothesis that a large number of common variants and genes with modest effects contribute to the risk of T2D and that current studies are underpowered to detect these effects. Indeed, despite the large sample sizes assembled here, a limitation of our study is that significant and borderline-significant associations based on combined analysis of the European IBC and

DIAGRAM datasets will need additional independent replication and follow-up.

Multiethnic meta-analysis across all 39 studies identified association of a common variant in *BCL2* with T2D, an anti-apoptotic protein that has not previously been implicated in this disease. Meta-analysis of IBC array studies in African Americans also identified study-wide-significant association of independent alleles at *HMGA2*, suggesting that this gene might be causal across different ethnicities. Our observations that a genetic risk score of 27 variants associates with a risk of T2D in African Americans, Asians, and Hispanic populations is also consistent with the idea that at least a subset of T2D causal risk alleles spans ethnicities. The genetic risk score analysis confirms and extends findings in a previous study by Waters et al.,³⁴ who report consistent association of 19 European T2D risk variants in several racial and ethnic groups from the US. Notably, our study included additional correction for population structure, which may contribute to the slightly reduced effect sizes observed.

In addition to common variants, the IBC array was selected to capture rare missense variants at select loci that are not directly captured or imputable by conventional GWASs. Robust association of an established missense SNP in *HNF1a* (rs1800574) with MAF = 0.029 ($p = 1.4 \times 10^{-7}$ in samples of European ancestry; Table S7)¹³ validates the platform's ability to detect rare variation that contributes to the risk of T2D. Although no rare variants reached study-wide significance, several follow-up candidate variants in known T2D loci were identified in African Americans.

In conclusion, this large-scale gene-centric meta-analysis of 39 multiethnic T2D association studies identified three European T2D risk loci (*GATAD2A/CILP2/PBX4*, previously known to have protective effects on lipids; *TH/INS*, previously known to have protective effects on T1D, and *SREBF1*), one African-American T2D risk locus (*HMGA2*), and one multiethnic risk locus (*BCL2*) and confirmed that a genetic score of T2D risk alleles influence risk of T2D in multiethnic populations including African-Americans, Hispanics, and Asians. Thus, well-powered, multiethnic GWASs of T2D should lead to the discovery of additional diabetes-associated genes relevant to multiple ethnic groups.

Supplemental Data

The Supplemental Data include acknowledgments and funding information for each cohort, a list of members of the DIAGRAM consortium and Look AHEAD research group, disclosures, nine tables, and two figures.

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Web Resources

The URLs for data presented herein are as follows:

Online Mendelian Inheritance in Man (OMIM), <http://www.omim.org>

MANTEL, <http://www.broadinstitute.org/~debakker/mantel.html>

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