

# Quantitative Trait Analysis of Type 2 Diabetes Susceptibility Loci Identified From Whole Genome Association Studies in the Insulin Resistance Atherosclerosis Family Study

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**OBJECTIVE**—Evaluate type 2 diabetes susceptibility variants identified from genome-wide association studies in Hispanic Americans and African Americans from the Insulin Resistance Atherosclerosis Family Study (IRAS-FS) for association with quantitative measures of glucose homeostasis and determine their biological role in vivo.

**RESEARCH DESIGN AND METHODS**—Seventeen type 2 diabetes-associated single nucleotide polymorphisms (SNPs) were genotyped in 1,268 Hispanic- and 581 African-American participants from the IRAS-FS. SNPs were tested for association with quantitative measures of glucose homeostasis, including insulin sensitivity index ( $S_I$ ), acute insulin response (AIR), and disposition index.

**RESULTS**—Previously identified risk variants in cyclin-dependent kinase 5 regulatory subunit associated protein 1-like 1 (*CDKAL1*) were associated with reduced AIR ( $P < 0.0046$ ) in Hispanic Americans. Additionally in Hispanic Americans, the variant in a hypothetical gene (chromosome 11; *LOC387761*) was significantly associated with AIR ( $P = 0.0046$ ) with the risk allele

showing protective effects, i.e., increased AIR. In both Hispanic and African-American populations, risk variants at the solute carrier family 30, member 8 (*SLC30A8*) locus were nominally associated with decreased disposition index ( $P < 0.078$ ). Risk variants in the insulin-like growth factor 2 mRNA-binding protein 2 (*IGF2BP2*) locus were associated with a decreased disposition index ( $P = 0.011$ ) exclusively in Hispanic Americans.

**CONCLUSIONS**—These data indicate a distinct, limited number of diabetes-related genes, more specifically the SNPs in the genes identified in European-derived populations, with modest evidence for association with glucose homeostasis traits in Hispanic Americans and African Americans. We observe evidence that diabetes risk for *CDKAL1*, *SLC30A8*, *IGF2BP2*, and *LOC387761* is specifically mediated through defects in insulin secretion. The mechanisms of other predisposing genes remain to be elucidated. *Diabetes* 57:1093–1100, 2008

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Received for publication 17 August 2007 and accepted in revised form 15 January 2008.

Published ahead of print at <http://diabetes.diabetesjournals.org> on 5 February 2008. DOI: 10.2337/db07-1169.

AIR, acute insulin response; *ALX4*, aristaless-like 4; *CDKAL1*, cyclin-dependent kinase 5 regulatory subunit associated protein 1-like 1; *CDKN2B/CDKN2A*, cyclin-dependent kinase inhibitor 2A/B; *EXT2*, exostosin 2; FSGT, frequently sampled intravenous glucose tolerance test; *FTO*, fat mass and obesity-associated; GWA, genome-wide association; *HHEX*, hematopoietically expressed homeobox; *IDE*, insulin-degrading enzyme; *IGF2BP2*, insulin-like growth factor 2 mRNA-binding protein 2; IRAS-FS, Insulin Resistance Atherosclerosis Family Study; *KIF11*, kinesin family member 11; MAF, minor allele frequency; *PKN2*, protein kinase N2;  $S_I$ , insulin sensitivity index; *SLC30A8*, solute carrier family 30, member 8; SNP, single nucleotide polymorphism.

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**T**ype 2 diabetes is a complex disease whose pathophysiology can be characterized by peripheral insulin resistance and reduced insulin secretion. Type 2 diabetes is a heritable disease (1), with multiple variants conferring modest risk to its polygenic inheritance (2). Prior investigations of the genetic determinants of type 2 diabetes have identified loci, each with relatively modest impacts on disease risk and whose impact has been difficult to replicate across studies (2).

Recent technical advances have facilitated genome-wide association (GWA) studies which can systematically and more comprehensively search the genome for disease susceptibility loci. Using this technique, novel etiological pathways of type 2 diabetes risk have been elucidated. Recently, four type 2 diabetes GWA studies have been reported (3–6). Taken together, these studies have identified 11 novel loci for involvement in type 2 diabetes susceptibility in European-derived populations. Of these 11 loci, 8 have been replicated across studies.

The purpose of this study was to evaluate variants within the 11 novel type 2 diabetes susceptibility loci identified from GWA studies in a large cohort of Hispanic Americans and African Americans from the Insulin Resistance Atherosclerosis Family Study (IRAS-FS). Quantitative trait analysis was performed to assess the impact of type 2 diabetes susceptibility variants identified in European-derived populations in these two ethnic minority populations. This analysis would enable the assessment of the metabolic pathway (i.e., insulin sensitivity or insulin secretion) through which these susceptibility genes act.

TABLE 1  
Demographic summary of IRAS-FS Hispanic-American and African-American participants

	Hispanic Americans			African Americans		
	<i>n</i>	Mean ± SD	Median	<i>n</i>	Mean ± SD	Median
Subjects	1,268			581		
<b>Demographics</b>						
Age (years)	1,268	42.8 ± 14.6	41.3	581	42.9 ± 14.0	41.5
Women (%)	746	58.8		344	59.2	
BMI (kg/m <sup>2</sup> )	1,258	28.9 ± 6.1	28.1	576	30.0 ± 6.8	29.0
Diabetes (%)	181	14.2		71	12.1	
<b>Glucose homeostasis</b>						
<i>S</i> <sub>I</sub> (×10 <sup>-5</sup> min <sup>-1</sup> /[pmol/l])	1,040	2.15 ± 1.86	1.7	500	1.63 ± 1.17	1.41
AIR (pmol/l)	1,040	760.2 ± 649.3	587.0	499	1,005.7 ± 826.2	771.5
Disposition index ( <i>S</i> <sub>I</sub> × AIR; × 10 <sup>-5</sup> min <sup>-1</sup> )	1,040	1,316.5 ± 1,236.012	1,005.2	499	1,425.7 ± 1,269.2	1,151.5
Fasting glucose (mg/dl)	1,101	93.4 ± 9.5	92.0	513	94.7 ± 9.7	93.0

**RESEARCH DESIGN AND METHODS**

**Recruitment.** Study design, recruitment, and phenotyping for IRAS-FS have been described previously in detail (7). Briefly, the IRAS-FS is a multicenter study designed to identify the genetic determinants of quantitative measures of glucose homeostasis. Members of large families of self-reported Hispanic ancestry (*n* = 1,268 individuals in 92 pedigrees from San Antonio, Texas, and San Luis Valley, Colorado) and African Americans (*n* = 581 individuals in 42 pedigrees from Los Angeles, California) were recruited. A clinical examination was performed that included an interview, a frequently sampled intravenous glucose tolerance test (FSIGT), anthropometric measurements, and blood collection. Specific to this report, measures of glucose homeostasis included those from the FSIGT using the reduced sampling protocol (8–10) calculated by mathematical modeling methods (MINMOD) (11): insulin sensitivity index (*S*<sub>I</sub>), acute insulin response (AIR), and disposition index. Distributions of the primary phenotypes are listed in Table 1.

**Genotyping.** Seventeen single nucleotide polymorphisms (SNPs) from 11 unique loci identified from type 2 diabetes GWA studies (3–6) were selected for analysis. Genotyping was performed on the Sequenom MassArray Genotyping System. Seventy blind duplicates were included to evaluate genotyping accuracy.

**Statistical analysis.** Initially, each SNP was examined for Mendelian inconsistencies using PedCheck (12). Genotypes inconsistent with Mendelian inheritance were converted to missing. Maximum likelihood estimates of allele frequencies were computed using the largest set of unrelated Hispanic- and African-American individuals (*n* = 229 and 58, respectively), and then genotypes were tested for departures from Hardy-Weinberg proportions.

To test for association between individual SNPs and each quantitative phenotype, variance component analysis was performed as implemented in SOLAR (13). When necessary, quantitative traits were transformed to best approximate the distributional assumptions of the test and minimize heterogeneity of the variance. For each phenotype, the 2 degrees of freedom test of genotypic association was performed. In addition, three individual contrasts defined by a priori genetic models (dominant, additive, and recessive) were computed (i.e., dominant model contrasts those with the polymorphism versus those without, additive model tests for a dose effect in the number of alleles, and recessive model contrasts individuals homozygous for the polymorphisms versus not). If the overall genotypic association was significant, the a priori contrasts were examined directly. If the overall genotypic association was not significant, the a priori contrasts were examined after adjusting for the three comparisons using a Bonferroni adjustment. This approach is consistent with the Fisher's protected least significant difference multiple comparisons procedure. Tests reported here were computed adjusting for age, sex, recruitment center, and BMI. Adjustments for multiple comparison tests were not performed because of selection of SNPs based on a priori hypotheses.

To examine the joint effect of these polymorphisms and their explanatory power for continuous traits, the model *R*<sup>2</sup> was computed. The *R*<sup>2</sup> statistic was calculated over just the covariates (i.e., age, sex, recruitment center, and BMI) and then with the inclusion of individual SNPs. In addition, stepwise model building was computed (i.e., forward selection with backward elimination) but did not provide additional explanatory information for these traits and SNPs (data not shown). Subjects with type 2 diabetes were excluded from the analysis of glucose homeostasis traits because overt diabetes and its treatment cause secondary changes in glycemic traits that obscure their underlying genetic determinants. SNP alleles were defined as "risk" or "protective" based on previous association studies of type 2 diabetes in European-derived populations (3–6).

**RESULTS**

This study evaluated 1,849 IRAS-FS participants, 1,268 Hispanic Americans and 581 African Americans. Table 1 summarizes descriptive statistics by ethnicity. On average, the Hispanic- and African-American participants had a similar proportion of women and comparable age and BMI values. Compared with African Americans, Hispanic Americans were more insulin sensitive (*S*<sub>I</sub> 2.15 vs. 1.63 × 10<sup>-5</sup> min<sup>-1</sup>/[pmol/l]; *P* = 0.013), had reduced insulin secretion (AIR 760 vs. 1,006 pmol/l; *P* < 0.001), and had a reduced disposition index (1,317 vs. 1,426 × 10<sup>-5</sup> min<sup>-1</sup>; *P* = 0.004). Marker genotyping success rates were 93.3–95.4% for the 17 SNPs examined, and blind duplicates were concordant. PedCheck analysis resulted in the exclusion of 11 of 34,527 genotypes. All SNPs were consistent with Hardy-Weinberg proportions in the Hispanic- and African-American populations.

The results of the quantitative trait analyses in Hispanic Americans are summarized in Table 2 and compared with the results of previous GWA studies from European-derived populations (3–6) in Table 3. The strongest evidence for association was observed with two SNPs (rs7754840, *P* = 0.0043, and rs10946398, *P* = 0.0046) in the intronic region of the cyclin-dependent kinase 5 regulatory subunit associated protein 1-like 1 (*CDKAL1*) gene with AIR. These SNPs showed the strongest evidence of association in the dominant model (Supplemental Table 1A, which is detailed in the online appendix [available at <http://dx.doi.org/10.2337/db07-1169>]; *P* = 0.0010 and 0.0011, respectively) with an 18.1% average decrease corresponding to 151 pmol/l insulin in the genotypic mean for AIR associated with the presence of the "risk" alleles C. The next strongest association was also observed with AIR for rs7480010 (*P* = 0.0046) in a hypothetical gene (chromosome 11; *LOC387761*). This SNP showed the strongest evidence of association in the additive model (Supplemental Table 1A; *P* = 0.0011) with an increase of 100 pmol/l (14.2%; genotype A/G) and 307 pmol/l (43.7%; genotype G/G) in the genotypic mean for AIR associated with the increasing copy number of the G allele. Notably, the G allele was previously denoted the "risk" allele in type 2 diabetes studies of European-derived populations because of increased prevalence of the allele in type 2 diabetes cases versus controls (5). Association at this locus was also seen with disposition index (*P* = 0.036) following an additive model (Supplemental Table 1A; *P* = 0.011) with an increase of 50 × 10<sup>-5</sup> min<sup>-1</sup> (3.9%; genotype A/G) and 353 × 10<sup>-5</sup> min<sup>-1</sup> (27.5%; genotype G/G) in the genotypic

TABLE 2

Quantitative trait analysis using the 2 degrees of freedom test for type 2 diabetes susceptibility loci with glucose homeostasis phenotypes in the IRAS-FS Hispanic-American cohort

Phenotype	Gene	SNP	Alleles*	MAF	Genotypic mean			P value	R <sup>2</sup> †	
					1/1	1/2	2/2			
S <sub>I</sub>	PKN2	rs6698181	C/T	0.41	2.00 ± 1.69 (371)	2.21 ± 1.94 (469)	2.33 ± 2.02 (149)	0.98	0.0001	
	IGFBP2	rs4402960	G/T	0.28	2.29 ± 1.97 (539)	2.01 ± 1.77 (382)	1.81 ± 1.29 (72)	0.21	0.0040	
	FLJ39370	rs17044137	T/A	0.19	2.13 ± 1.83 (661)	2.15 ± 1.85 (292)	2.88 ± 2.43 (41)	0.81	0.0004	
	CDKAL1	rs7754840	G/C	0.34	2.07 ± 1.77 (467)	2.20 ± 1.89 (432)	2.43 ± 2.27 (92)	0.13	0.0014	
		rs10946398	A/C	0.34	2.08 ± 1.77 (470)	2.19 ± 1.87 (438)	2.43 ± 2.27 (92)	0.14	0.0014	
	SLC30A8	rs13266634	C/T	0.25	2.12 ± 1.82 (590)	2.18 ± 1.90 (370)	2.36 ± 2.14 (46)	0.84	0.0002	
	CDKN2A/2B	rs10811661	T/C	0.12	2.18 ± 1.91 (774)	2.10 ± 1.72 (213)	1.70 ± 1.08 (8)	1.00	0.0002	
		rs564398	T/C	0.19	2.24 ± 1.86 (675)	1.99 ± 1.85 (291)	1.78 ± 2.07 (28)	0.81	0.0004	
	IDE/KIF11/HHEX	rs1111875	C/T	0.35	2.18 ± 1.83 (479)	2.17 ± 1.94 (445)	2.06 ± 1.66 (91)	0.42	0.0000	
		rs5015480	T/C	0.46	2.10 ± 1.90 (245)	2.23 ± 1.91 (497)	2.08 ± 1.76 (248)	0.12	0.0029	
		rs7923837	G/A	0.43	2.06 ± 1.84 (344)	2.22 ± 1.86 (492)	2.17 ± 1.95 (159)	0.39	0.0017	
	LOC387761	rs7480010	A/G	0.28	2.24 ± 1.85 (551)	2.03 ± 1.89 (356)	2.26 ± 1.90 (78)	0.99	0.0004	
	Intragenic	rs9300039	C/A	0.09	2.22 ± 1.92 (874)	1.72 ± 1.44 (116)	1.92 ± 0.59 (8)	0.10	0.0032	
	EXT2/ALX4	rs3740878	T/C	0.43	2.09 ± 1.70 (337)	2.16 ± 1.97 (506)	2.25 ± 1.88 (149)	0.95	0.0000	
		rs11037909	T/C	0.43	2.10 ± 1.69 (339)	2.16 ± 1.97 (495)	2.27 ± 1.89 (149)	0.92	0.0000	
		rs1113132	G/C	0.43	2.09 ± 1.70 (338)	2.17 ± 1.98 (503)	2.26 ± 1.89 (147)	0.96	0.0000	
		FTO	rs8050136	C/A	0.23	2.18 ± 1.86 (586)	2.09 ± 1.80 (346)	2.35 ± 2.34 (58)	0.40	0.0000
	AIR	PKN2	rs6698181	C/T	0.41	719 ± 587 (371)	776 ± 685 (469)	849 ± 701 (149)	0.63	0.0005
		IGFBP2	rs4402960	G/T	0.28	780 ± 678 (539)	763 ± 678 (382)	696 ± 620 (72)	0.46	0.0039
		FLJ39370	rs17044137	T/A	0.19	795 ± 679 (661)	718 ± 611 (292)	573 ± 407 (41)	0.14	0.0040
CDKAL1		rs7754840	G/C	0.34	834 ± 701 (467)	719 ± 590 (432)	649 ± 644 (92)	0.0043	0.0123	
		rs10946398	A/C	0.34	836 ± 709 (470)	719 ± 588 (438)	649 ± 644 (92)	0.0046	0.0123	
SLC30A8		rs13266634	C/T	0.25	721 ± 599 (590)	827 ± 710 (370)	874 ± 815 (46)	0.084	0.0056	
CDKN2A/2B		rs10811661	T/C	0.12	759 ± 639 (774)	777 ± 697 (213)	1,035 ± 576 (8)	0.60	0.0000	
		rs564398	T/C	0.19	759 ± 632 (675)	785 ± 681 (291)	764 ± 816 (28)	0.47	0.0004	
IDE/KIF11/HHEX		rs1111875	C/T	0.35	733 ± 654 (479)	796 ± 659 (445)	715 ± 571 (91)	0.77	0.0000	
		rs5015480	T/C	0.46	812 ± 624 (245)	754 ± 673 (497)	730 ± 640 (248)	0.40	0.0000	
		rs7923837	G/A	0.43	773 ± 670 (344)	743 ± 650 (492)	829 ± 618 (159)	0.15	0.0000	
LOC387761		rs7480010	A/G	0.28	703 ± 610 (551)	803 ± 647 (356)	1,010 ± 842 (78)	0.0046	0.0196	
Intragenic		rs9300039	C/A	0.09	749 ± 628 (874)	894 ± 807 (116)	599 ± 315 (8)	0.65	0.0012	
EXT2/ALX4		rs3740878	T/C	0.43	720 ± 583 (337)	817 ± 707 (506)	709 ± 592 (149)	0.11	0.0002	
		rs11037909	T/C	0.43	721 ± 582 (339)	816 ± 713 (495)	706 ± 593 (149)	0.12	0.0001	
		rs1113132	G/C	0.43	721 ± 583 (338)	819 ± 714 (503)	694 ± 568 (147)	0.10	0.0002	
		FTO	rs8050136	C/A	0.23	755 ± 614 (586)	811 ± 740 (346)	311 ± 408 (58)	0.26	0.0002
Disposition index		PKN2	rs6698181	C/T	0.41	1,202 ± 1,137 (371)	1,313 ± 1,168 (469)	1,624 ± 1,605 (149)	0.42	0.0007
		IGFBP2	rs4402960	G/T	0.28	1,441 ± 1,280 (539)	1,220 ± 1,225 (382)	1,058 ± 1,006 (72)	0.011	0.0128
		FLJ39370	rs17044137	T/A	0.19	1,364 ± 1,263 (661)	1,199 ± 1,028 (292)	1,668 ± 2,068 (41)	0.094	0.0015
	CDKAL1	rs7754840	G/C	0.34	1,339 ± 1,234 (467)	1,302 ± 1,182 (432)	1,429 ± 1,561 (92)	0.22	0.0003	
		rs10946398	A/C	0.34	1,342 ± 1,241 (470)	1,300 ± 1,181 (438)	1,429 ± 1,561 (92)	0.21	0.0003	
	SLC30A8	rs13266634	C/T	0.25	1,240 ± 1,177 (590)	1,446 ± 1,293 (370)	1,529 ± 1,607 (46)	0.078	0.0054	
	CDKN2A/2B	rs10811661	T/C	0.12	1,348 ± 1,303 (774)	1,262 ± 1,035 (213)	1,439 ± 689 (8)	0.55	0.0007	
		rs564398	T/C	0.19	1,404 ± 1,328 (675)	1,187 ± 1,032 (291)	1,023 ± 1,072 (28)	0.93	0.0017	
	IDE/KIF11/HHEX	rs1111875	C/T	0.35	1,299 ± 1,288 (479)	1,381 ± 1,221 (445)	1,226 ± 1,091 (91)	0.26	0.0000	
		rs5015480	T/C	0.46	1,361 ± 1,176 (245)	1,344 ± 1,296 (497)	1,243 ± 1,198 (248)	0.21	0.0028	
		rs7923837	G/A	0.43	1,274 ± 1,190 (344)	1,327 ± 1,276 (492)	1,453 ± 1,272 (159)	0.11	0.0014	
	LOC387761	rs7480010	A/G	0.28	1,284 ± 1,220 (551)	1,334 ± 1,225 (356)	1,637 ± 1,443 (78)	0.036	0.0076	
	Intragenic	rs9300039	C/A	0.09	1,330 ± 1,246 (874)	1,316 ± 1,220 (116)	1,045 ± 427 (8)	0.40	0.0000	
	EXT2/ALX4	rs3740878	T/C	0.43	1,288 ± 1,189 (337)	1,374 ± 1,308 (506)	1,260 ± 1,118 (149)	0.54	0.0000	
		rs11037909	T/C	0.43	1,289 ± 1,186 (339)	1,370 ± 1,316 (495)	1,257 ± 1,117 (149)	0.57	0.0000	
		rs1113132	G/C	0.43	1,288 ± 1,188 (338)	1,380 ± 1,314 (503)	1,240 ± 1,107 (147)	0.48	0.0000	
		FTO	rs8050136	C/A	0.23	1,362 ± 1,286 (586)	1,296 ± 1,199 (346)	1,223 ± 1,139 (58)	0.99	0.0000

Data are means ± SD (*n*). \*Major/minor alleles determined from the maximal set of unrelated individuals (*n* = 229). Risk allele, identified from previous studies (3–6), is underlined. †Variance proportion over baseline of the quantitative trait explained by inclusion of the SNP in the model.

mean for disposition index associated with the increasing number of G alleles. In addition, SNP rs4402960 in the intronic region of insulin-like growth factor 2 mRNA-

binding protein 2 (*IGF2BP2*) was associated with disposition index (*P* = 0.011). This SNP showed the strongest association in the additive model (Supplemental Table 1A;

TABLE 3  
Comparison of significant findings from the IRAS-FS Hispanic-American population with previous studies in European-derived populations (3–6)

Previously published GWA studies		IRAS-FS Hispanic Americans				Genotypic means					
SNP	Risk Allele	Sladek et al.†	Saxena et al.‡	Scott et al.§	Zeggini et al.¶	Minor Allele Frequency	Trait	P value	1/1	1/2	2/2
	Frequency*	et al.†	et al.‡	et al.§	et al.¶	Frequency		2df			
<i>IGFBP2</i>											
rs4402960	T	0.29	1.17 (1.11–1.23)	1.18 (1.08–1.28)	1.11 (1.05–1.16)	T	$S_1$	0.21	2.29 ± 1.97 (539)	2.01 ± 1.77 (382)	1.81 ± 1.29 (72)
							AIR	0.46	780 ± 678 (539)	763 ± 678 (382)	696 ± 620 (72)
							Disposition index	0.011	1,441 ± 1,280 (539)	1,220 ± 1,225 (382)	1,058 ± 1,006 (72)
<i>CDKALI</i>											
rs7754840	C	0.31	1.08 (1.03–1.14)	1.12 (1.03–1.22)		C	$S_1$	0.13	2.07 ± 1.77 (467)	2.20 ± 1.89 (432)	2.43 ± 2.27 (92)
							AIR	0.0043	834 ± 701 (467)	719 ± 590 (432)	649 ± 644 (92)
							Disposition index	0.22	1,339 ± 1,234 (467)	1,302 ± 1,182 (432)	1,429 ± 1,561 (92)
rs10946398	C	0.31			1.16 (1.10–1.22)	C	$S_1$	0.14	2.08 ± 1.77 (470)	2.19 ± 1.87 (438)	2.43 ± 2.27 (92)
							AIR	0.0046	836 ± 709 (470)	719 ± 588 (438)	649 ± 644 (92)
							Disposition index	0.21	1,342 ± 1,241 (470)	1,300 ± 1,181 (438)	1,429 ± 1,561 (92)
Hypothetical gene ( <i>LOC387761</i> )											
rs7480010	G	0.25	1.40 ± 0.25	1.03		G	$S_1$	0.99	2.24 ± 1.85 (551)	2.03 ± 1.89 (356)	2.26 ± 1.90 (78)
							AIR	0.0046	703 ± 610 (551)	803 ± 647 (356)	1,010 ± 842 (78)
							Disposition index	0.036	1,284 ± 1,220 (551)	1,334 ± 1,225 (356)	1,637 ± 1,443 (78)

Data are OR, OR (95% CI), or means ± SD ( $n$ ). 2df, 2 degrees of freedom. †Hapmap CEU MAFs. ‡Ref. 5 ( $n$  = 2,617 case subjects/2,894 control subjects). †Ref. 3 ( $n$  = 6,529 case subjects/7,252 control subjects). §Ref. 4 ( $n$  = 2,376 case subjects/2,432 control subjects). ¶Ref. 6 ( $n$  = 5,681 case subjects/8,284 control subjects).

$P$  = 0.0031) with a decrease of  $221 \times 10^{-5} \text{ min}^{-1}$  (15.3%; genotype G/T) and  $383 \times 10^{-5} \text{ min}^{-1}$  (26.6%; genotype T/T) in the genotypic mean for disposition index associated with number of the “risk” allele T. The SNPs evaluated explained, on average, <1% of the variance ( $R^2$ ) for the three quantitative traits examined ( $R^2$ ; Table 2). Analysis of SNPs in the other eight loci, protein kinase N2 (*PKN2*), a hypothetical gene (*FLJ39370*), solute carrier family 30, member 8 (*SLC30A8*), cyclin-dependent kinase inhibitor 2A/B (*CDKN2B/CDKN2A*), the insulin-degrading enzyme (*IDE*)/kinesin family member 11 (*KIF11*)/hematopoietically expressed homeobox (*HHEX*) gene cluster, an intragenic region on chromosome 11, the exostosin 2 (*EXT2*)/aristaless-like 4 (*ALX4*) gene region, and fat mass- and obesity-associated (*FTO*), did not show any evidence of association in the Hispanic-American subjects.

In African Americans (Tables 4 and 5, study comparisons), the strongest evidence for association was observed between two SNPs (rs7754840,  $P$  = 0.049, and rs10946398,  $P$  = 0.063) in the *CDKALI* gene and  $S_1$ . These SNPs showed the strongest evidence of association in the additive model (Supplemental Table 1B;  $P$  = 0.016 and 0.027, respectively) with an average decrease of  $0.24 \times 10^{-5} \text{ min}^{-1}/[\text{pmol/l}]$  (12.9%; genotype G/C) and  $0.33 \times 10^{-5} \text{ min}^{-1}/[\text{pmol/l}]$  (17.5%; genotype C/C) in the genotypic mean for  $S_1$  associated with the number of “risk” alleles C. Two additional loci showed evidence for association with disposition index. A nonsynonymous SNP, rs13266634 ( $P$  = 0.050), in the *SLC30A8* gene was associated with disposition index following an additive model (Supplemental Table 1B;  $P$  = 0.021). The “risk” allele C was associated with a  $1,011 \times 10^{-5} \text{ min}^{-1}$  (38.9%; genotype T/C) and  $1,236 \times 10^{-5} \text{ min}^{-1}$  (47.5%; genotype C/C) decrease in disposition index associated with the number of “risk” alleles. SNP rs7923837, downstream of the *IDE/KIF11/HHEX* gene cluster, was modestly associated with disposition index ( $P$  = 0.045) following an additive model (Supplemental Table 1B;  $P$  = 0.024). The “risk” allele G was associated with a  $505 \times 10^{-5} \text{ min}^{-1}$  (64.4%; genotype A/G) and  $664 \times 10^{-5} \text{ min}^{-1}$  (84.7%; genotype G/G) increase in disposition index associated with the number of risk alleles. The SNPs evaluated explained, on average, <1% of the variance ( $R^2$ ) for the three quantitative traits examined ( $R^2$ ; Table 4). Analysis of SNPs in the other eight genes, *PKN2*, *IGF2BP2*, *FLJ39370*, *CDKN2B/CDKN2A*, *LOC387761*, intragenic region on chromosome 11, *EXT2/ALX4*, and *FTO*, did not show any evidence of association in the African-American subjects.

DISCUSSION

Quantitative trait analysis results of glucose homeostasis phenotypes differed dramatically between the two populations examined (Tables 2 and 4). The most striking associations observed in the Hispanic American population were at the *CDKALI* locus. Two highly correlated SNPs (rs7754840 and rs10946398;  $r^2$  = 1.0) were associated significantly with  $\beta$ -cell function as measured by AIR ( $P$  < 0.0046). Genotypic means for AIR were consistent with the “risk” alleles C having a reduced AIR following a dominant model ( $P$  < 0.0011). In African Americans, there was a dramatic difference in minor allele frequency (MAF) for these SNPs (C allele; 0.63 vs. 0.34 in Hispanic Americans), and associations at this locus were limited to nominal association with  $S_1$  ( $P$  < 0.063). Genotypic means associated with the “risk” allele C had a decreased  $S_1$

TABLE 4  
Quantitative trait analysis using the 2 degrees of freedom test for type 2 diabetes susceptibility loci with glucose homeostasis phenotypes in the IRAS-FS African-American cohort

Phenotype	Gene	SNP	Alleles*	MAF	Genotypic means			P value	R <sup>2</sup> †	
					1/1	1/2	2/2			
S <sub>I</sub>	PKN2	rs6698181	C/T	0.19	1.63 ± 1.22 (333)	1.71 ± 1.16 (108)	1.21 ± 0.68 (16)	0.52	0.0000	
	IGFBP2	rs4402960	G/T	0.50	1.60 ± 1.23 (103)	1.65 ± 1.10 (231)	1.62 ± 1.27 (124)	0.86	0.0000	
	FLJ39370	rs17044137	T/A	0.40	1.59 ± 1.07 (200)	1.63 ± 1.27 (200)	1.76 ± 1.22 (62)	0.43	0.0001	
	CDKAL1	rs7754840	C/G	0.37	1.52 ± 1.06 (148)	1.62 ± 1.13 (228)	1.85 ± 1.41 (82)	0.049	0.0062	
		rs10946398	C/A	0.38	1.54 ± 1.10 (148)	1.61 ± 1.13 (231)	1.86 ± 1.41 (81)	0.063	0.0067	
	SLC30A8	rs13266634	C/T	0.11	1.59 ± 1.12 (366)	1.80 ± 1.44 (93)	1.98 ± 1.14 (6)	0.43	0.0021	
	CDKN2A/2B	rs10811661	T/C	0.09	1.59 ± 1.16 (395)	1.86 ± 1.17 (62)	2.40 ± 2.36 (4)	0.50	0.0025	
		rs564398	T/C	0.07	1.64 ± 1.22 (383)	1.60 ± 1.04 (81)	1.58 ± 0.00 (1)	0.94	0.0000	
	IDE/KIF11/HHEX	rs1111875	C/T	0.22	1.60 ± 1.12 (282)	1.63 ± 1.17 (176)	1.85 ± 1.51 (29)	0.44	0.0001	
		rs5015480	C/T	0.34	1.63 ± 1.16 (161)	1.62 ± 1.16 (217)	1.63 ± 1.28 (79)	0.88	0.0000	
		rs7923837	G/A	0.06	1.64 ± 1.16 (395)	1.64 ± 1.36 (66)	1.26 ± 1.42 (4)	0.61	0.0001	
	LOC387761	rs7480010	G/A	0.17	1.54 ± 1.15 (342)	1.84 ± 1.23 (111)	2.35 ± 0.92 (7)	0.07	0.0092	
	Intragenic	rs9300039	C/A	0.18	1.69 ± 1.22 (348)	1.49 ± 1.07 (96)	1.50 ± 1.24 (11)	0.37	0.0045	
	EXT2/ALX4	rs3740878	T/C	0.13	1.61 ± 1.20 (370)	1.72 ± 1.07 (89)	0.98 ± 0.33 (3)	0.86	0.0000	
		rs11037909	T/C	0.17	1.60 ± 1.19 (334)	1.75 ± 1.20 (112)	1.48 ± 0.62 (12)	0.57	0.0000	
		rs1113132	G/C	0.12	1.62 ± 1.21 (376)	1.68 ± 1.07 (83)	0.98 ± 0.33 (3)	0.92	0.0008	
		rs8050136	A/C	0.49	1.72 ± 1.14 (105)	1.58 ± 1.16 (221)	1.67 ± 1.25 (135)	0.11	0.0070	
	AIR	PKN2	rs6698181			985 ± 832 (332)	1,040 ± 883 (108)	1,032 ± 841 (16)	0.93	0.0000
		IGFBP2	rs4402960	G/T	0.50	1,056 ± 884 (103)	982 ± 830 (230)	1,007 ± 849 (124)	0.87	0.0001
		FLJ39370	rs17044137	T/A	0.40	1,047 ± 810 (200)	1,008 ± 907 (200)	893 ± 739 (61)	0.38	0.0010
CDKAL1		rs7754840	C/G	0.37	1,011 ± 769 (147)	1,063 ± 903 (228)	823 ± 745 (82)	0.14	0.0055	
		rs10946398	C/A	0.38	1,011 ± 769 (147)	1,064 ± 915 (231)	828 ± 749 (81)	0.15	0.0054	
SLC30A8		rs13266634	C/T	0.11	1,014 ± 872 (365)	962 ± 720 (93)	1,198 ± 892 (6)	0.81	0.0003	
CDKN2A/2B		rs10811661	T/C	0.09	1,011 ± 870 (394)	991 ± 698 (62)	733 ± 583 (4)	0.99	0.0001	
		rs564398	T/C	0.07	1,020 ± 858 (382)	831 ± 777 (81)	1,041 ± 0 (1)	0.91	0.0052	
IDE/KIF11/HHEX		rs1111875	C/T	0.22	1,106 ± 902 (282)	877 ± 643 (175)	970 ± 1,032 (29)	0.12	0.0155	
		rs5015480	C/T	0.34	1,019 ± 896 (160)	981 ± 788 (217)	1,063 ± 906 (79)	0.34	0.0000	
		rs7923837	G/A	0.06	1,027 ± 851 (394)	903 ± 809 (66)	444 ± 326 (4)	0.063	0.0178	
LOC387761		rs7480010	G/A	0.17	1,037 ± 838 (341)	944 ± 889 (111)	571 ± 278 (7)	0.33	0.0044	
Intragenic		rs9300039	C/A	0.18	991 ± 813 (347)	1,037 ± 944 (96)	1,251 ± 1,062 (11)	0.28	0.0035	
EXT2/ALX4		rs3740878	T/C	0.13	1,008 ± 837 (369)	1,007 ± 894 (89)	1,087 ± 378 (3)	0.88	0.0004	
		rs11037909	T/C	0.17	1,010 ± 851 (333)	966 ± 836 (112)	1,196 ± 929 (12)	0.70	0.0008	
		rs1113132	G/C	0.12	999 ± 834 (375)	1,040 ± 912 (83)	1,087 ± 378 (3)	0.66	0.0002	
		rs8050136	A/C	0.49	1,052 ± 865 (105)	1,025 ± 858 (220)	937 ± 814 (135)	0.53	0.0011	
Disposition index		PKN2	rs6698181			1,378 ± 1,292 (332)	1,497 ± 1,250 (108)	1,329 ± 1,094 (16)	0.75	0.0009
		IGFBP2	rs4402960	G/T	0.50	1,584 ± 1,645 (103)	1,347 ± 1,102 (230)	1,415 ± 1,272 (124)	0.80	0.0001
		FLJ39370	rs17044137	T/A	0.40	1,471 ± 1,244 (200)	1,342 ± 1,212 (200)	1,540 ± 1,655 (61)	0.25	0.0000
	CDKAL1	rs7754840	C/G	0.37	1,382 ± 1,190 (147)	1,478 ± 1,347 (228)	1,325 ± 1,316 (82)	0.44	0.0000	
		rs10946398	C/A	0.38	1,384 ± 1,185 (147)	1,466 ± 1,338 (231)	1,338 ± 1,319 (81)	0.54	0.0000	
	SLC30A8	rs13266634	C/T	0.11	1,364 ± 1,203 (365)	1,589 ± 1,491 (93)	2,600 ± 2,276 (6)	0.050	0.0032	
	CDKN2A/2B	rs10811661	T/C	0.09	1,402 ± 1,308 (394)	1,511 ± 1,120 (62)	1,237 ± 711 (4)	0.87	0.0011	
		rs564398	T/C	0.07	1,439 ± 1,334 (382)	1,326 ± 1,042 (81)	1,645 ± 0 (1)	0.97	0.0023	
	IDE/KIF11/HHEX	rs1111875	C/T	0.22	1,524 ± 1,397 (282)	1,310 ± 1,083 (175)	1,346 ± 1,113 (29)	0.094	0.0067	
		rs5015480	C/T	0.34	1,359 ± 1,244 (160)	1,436 ± 1,337 (217)	1,495 ± 1,259 (79)	0.21	0.0009	
		rs7923837	G/A	0.06	1,448 ± 1,297 (394)	1,289 ± 1,223 (66)	784 ± 1,116 (4)	0.045	0.0100	
	LOC387761	rs7480010	G/A	0.17	1,366 ± 1,273 (341)	1,558 ± 1,324 (111)	1,243 ± 554 (7)	0.56	0.0016	
	Intragenic	rs9300039	C/A	0.18	1,484 ± 1,361 (347)	1,255 ± 1,061 (96)	1,417 ± 1,184 (11)	0.71	0.0011	
	EXT2/ALX4	rs3740878	T/C	0.13	1,411 ± 1,316 (369)	1,458 ± 1,151 (89)	1,017 ± 385 (3)	0.74	0.0001	
		rs11037909	T/C	0.17	1,408 ± 1,335 (333)	1,382 ± 1,093 (112)	1,679 ± 1,356 (12)	0.48	0.0002	
		rs1113132	G/C	0.12	1,410 ± 1,319 (375)	1,472 ± 1,170 (83)	1,017 ± 385 (3)	0.66	0.0006	
		rs8050136	A/C	0.49	1,534 ± 1,299 (105)	1,369 ± 1,152 (220)	1,420 ± 1,482 (135)	0.16	0.0046	

Data are means ± SD (n). \*Major/minor alleles determined from the maximal set of unrelated individuals (n = 229). Risk allele, identified from previous studies (3–6), is underlined. †Variance proportion over baseline of the quantitative trait explained by inclusion of the SNP in the model.

following an additive model (P < 0.027), which is consistent with previous reports (3,14). This difference in trait association may reflect the significant biological differences observed between the African- and Hispanic-American subjects with regard to S<sub>I</sub> and AIR, as seen in Table 1. Results of this association could also reflect pleiotropy,

TABLE 5  
Comparison of significant findings from the IRAS-FS African-American population with previous studies in European-derived populations (3–6)

SNP	Previously published GWA studies		Zeggini et al.¶	Scott et al.§	Saxena et al.‡	Shadek et al.†	Allele	Risk Frequency*	Minor Allele Frequency		Trait	Genotypic means	
	Allele	Risk Frequency*							Allele	Frequency		1/1	1/2
<i>CDKALI</i>													
rs7754840	C	0.31	1.08 (1.03–1.14)	1.12 (1.03–1.22)	G	0.37	$S_i$ AIR	0.049 0.14	1.52 ± 1.06 (148) 1,011 ± 769 (147)	1.62 ± 1.13 (228) 1,063 ± 903 (228)	$S_i$ Disposition index	1.85 ± 1.41 (82) 823 ± 745 (82)	
rs10946398	C	0.31	1.16 (1.10–1.22)	1.16 (1.10–1.22)	A	0.38	$S_i$ AIR	0.063 0.15	1.54 ± 1.10 (148) 1,011 ± 769 (147)	1.61 ± 1.13 (231) 1,064 ± 915 (231)	$S_i$ Disposition index	1,325 ± 1,316 (82) 1.86 ± 1.41 (81) 828 ± 749 (81)	
<i>SLC30A8</i>													
rs13266634	C	0.75	1.53 ± 0.31	1.18 (1.09–1.29)	T	0.11	$S_i$ AIR	0.43 0.81	1.59 ± 1.12 (366) 1,014 ± 872 (365)	1.80 ± 1.44 (93) 962 ± 720 (93)	$S_i$ Disposition index	1.98 ± 1.14 (6) 1,198 ± 892 (6)	
<i>ID1/KIF11/HHEX</i>													
rs1111875	C	0.56	1.44 ± 0.24	1.10 (1.01–1.19)	T	0.22	$S_i$ AIR	0.44 0.12	1.60 ± 1.12 (282) 1,106 ± 902 (282)	1.63 ± 1.17 (176) 877 ± 643 (175)	$S_i$ Disposition index	1.85 ± 1.51 (29) 970 ± 1032 (29)	
rs5015480	C	0.45	1.13 (1.07–1.19)	1.13 (1.07–1.19)	T	0.34	$S_i$ AIR	0.88 0.34	1.63 ± 1.16 (161) 1,019 ± 896 (160)	1.62 ± 1.16 (217) 981 ± 788 (217)	$S_i$ Disposition index	1,346 ± 1,113 (29) 1.63 ± 1.28 (79) 1,063 ± 906 (79)	
rs7923837	A	0.37	1.45 ± 0.25	1.45 ± 0.25	A	0.06	$S_i$ AIR	0.21 0.61	1.359 ± 1,244 (160) 1,64 ± 1.16 (395)	1,436 ± 1,337 (217) 1.64 ± 1.36 (66)	$S_i$ Disposition index	1,495 ± 1,259 (79) 1.26 ± 1.42 (4) 444 ± 325 (4)	

Data are OR, OR (95% CI), or means ± SD, 2 df, 2 degrees of freedom. \*Hapmap CEU MAFs. †Ref. 5 ( $n = 2,617$  case subjects/2,894 control subjects). ‡Ref. 3 ( $n = 6,529$  case subjects/7,252 control subjects). §Ref. 4 ( $n = 2,376$  case subjects/2,432 control subjects). ¶Ref. 6 ( $n = 5,681$  case subjects/8,284 control subjects).

however, the genetic correlation between  $S_1$  and AIR in the African American subjects is  $-0.09 \pm 0.23$ , which is inconsistent with this hypothesis.

Similar to the results of association analysis with *CDKALI*, a variant in a hypothetical locus (*LOC387761*) was associated with different phenotypes in the two populations examined. In Hispanic Americans, the previously identified “risk” allele G of rs7480010 was significantly associated with an increased AIR ( $P = 0.0046$ ) and modestly associated with an increased disposition index ( $P = 0.036$ ). These traits are mathematically related (disposition index =  $S_1 \times$  AIR) and have a genetic correlation in these Hispanic-American subjects of  $0.68 \pm 0.07$ . In African Americans, there is a trend toward association at this locus with decreased  $S_1$  ( $P = 0.068$ ) corresponding to the “risk” allele. The confounding associations observed at the *CDKALI* and *LOC387761* loci could be attributed partially to the dramatic difference in MAF between Hispanic Americans and African Americans which raises the possibility that the identified susceptibility variant is not causal but exhibits effects via linkage disequilibrium, patterns which are different between populations. These are the only two loci that were associated with quantitative measures of glucose homeostasis in both populations in this study, although they have contrasting evidence of phenotypic association across populations. In addition, it is worth noting that the Hispanic- and African-American cohorts examined are phenotypically diverse in terms of glucose homeostasis parameters with African Americans having a significantly lower  $S_1$  ( $P = 0.013$ ) and higher AIR ( $P < 0.001$ ). Therefore, the lack of a compensatory increase in AIR observed in the African-American cohort in the presence of a significantly decreased  $S_1$  could be attributed to an already increased baseline AIR.

At the *SLC30A8* locus, a nonsynonymous variant (R325W; rs13266634) was associated with variation in the disposition index in the African-American cohorts ( $P = 0.050$ ) and more modestly in the Hispanic-American ( $P = 0.078$ ) cohorts. The “risk” allele C, identified and replicated across all four GWA studies (3–6), was associated with a reduced disposition index ( $P = 0.05$ ) following an additive genetic model ( $P = 0.021$ ). Of the loci examined, variation at the *SLC30A8* locus represents the only evidence of consistent association with the GWA reports (3–6) as to the direction of “risk” and consistent findings in the two non-European-origin populations examined herein.

Association observed at the *IGF2BP2* locus was limited to the Hispanic-American cohort. SNP rs4402960 was associated with alteration of the disposition index with the “risk” allele T, as determined from the GWA reports (3–6), at a comparable frequency compared with estimates from the European-derived populations and associated with reduced disposition index ( $P = 0.011$ ) following an additive model ( $P = 0.0031$ ). Lack of association with glucose homeostasis phenotypes in the African-American population could be attributed to a substantially increased diabetes “risk” allele frequency (MAF = 0.50) and linkage disequilibrium block boundaries, which differ between the European-American and African populations as suggested from HapMap data.

In addition, evidence for association of variants located downstream of the *IDE/KIF11/HHEX* gene cluster was limited to a single SNP (rs7923837) associated modestly with disposition index ( $P = 0.045$ ) exclusively in the African American population. Proposed susceptibility variants in *PKN2*, *FLJ39370*, *CDKN2A/CDKN2B*, an intra-

genic region on chromosome 11, *EXT2/ALX4*, and *FTO* failed to show evidence of association with the measures of glucose homeostasis evaluated in either ethnic group.

Although the IRAS-FS was designed to study quantitative traits related to glucose homeostasis (7), there were additional subjects with type 2 diabetes in these families, which allowed us to perform association analysis of the 17 GWA SNPs with type 2 diabetes as a qualitative trait. Likely reflecting the relatively modest numbers of those affected by type 2 diabetes in IRAS-FS (181 Hispanic Americans and 71 African Americans), results were inconsistent and largely nonsignificant (Supplemental Tables 2A and 2B). In Hispanic Americans, a single SNP (rs9300039) in an intragenic region on chromosome 11 was found to be associated with type 2 diabetes ( $P = 0.039$ ; Supplemental Table 2A). The A allele of SNP rs9300039 had an odds ratio (OR) of 0.49 (95% CI 0.25–0.96) and therefore was found to be associated with protection from type 2 diabetes. Scott et al. (4) found association of the C allele with type 2 diabetes “risk”, 1.48 (1.28–1.71), but this result failed to replicate in the companion publications (3,6). In the African American population, a single SNP (rs4402960) in *IGF2BP2* was significantly associated with type 2 diabetes as a qualitative trait ( $P = 0.021$ ; Supplemental Table 2B). The T allele of SNP rs4402960 was associated with protection from type 2 diabetes, 0.59 (0.38–0.92). This finding is inconsistent with three GWA publications (3,4,6), which found this allele to be associated with type 2 diabetes “risk” (meta analysis OR 1.14). The difference in directionality of association could be due to a marked difference in MAF between African-American (MAF = 0.50) and European-derived (MAF = 0.30) populations, which is consistent with HapMap estimates of allele frequency and linkage disequilibrium structural differences. As noted above, there is modest power given the sample size (Supplemental Table 3), nominal  $P$  values, and limited evidence that these SNPs contribute to differential type 2 diabetes risk in an independent African-American type 2 diabetes case/control sample (J. Lewis, personal communication). These results suggest these type 2 diabetes results should be viewed as preliminary findings in these populations and any conclusions on the genetic basis of clinical diabetes are not warranted from these data alone.

The IRAS-FS was designed to determine the underlying genetic and environmental contributors to insulin resistance and more broadly glucose homeostasis through quantitative trait analysis. The availability of high-quality metabolic testing in the IRAS-FS, which few studies have, facilitates interrogation of metabolic pathways through which loci implicated in type 2 diabetes susceptibility may influence glucose metabolism. This, taken together with the recruitment of multigenerational pedigrees, with attendant significant increase in power over a sibpair study design, enhance the ability of IRAS-FS to detect and comprehensively evaluate genes related to glucose homeostasis and, in turn, type 2 diabetes. Taken together, the results of the association analyses reported here suggest that a small number of type 2 diabetes susceptibility loci, *CDKALI*, *LOC387761*, *SLC30A8*, and *IGF2BP2*, identified from studies in European-derived type 2 diabetes populations, contribute modestly to variation in glucose homeostasis in Hispanic Americans and African Americans. The balance of the associations with measures of glucose homeostasis suggest that the *CDKALI*, *LOC387761*, *SLC30A8*, and *IGF2BP2* loci are contributing to diabetes susceptibility primarily through effects on insulin secre-

tion as measured by AIR or through homeostatic regulation of the balance of insulin secretion and insulin sensitivity. Any strong evidence for association with insulin sensitivity, a primary component of diabetes susceptibility, is strikingly absent. Therefore, further research for genes effecting insulin sensitivity is in order.

#### ACKNOWLEDGMENTS

This research was supported in part by NIH grants HL060894, HL060931, HL060944, HL061019, and HL061210.

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