

**Quantitative Trait Analysis of T2D Susceptibility Loci Identified from Whole Genome Association Studies in the IRAS Family Study**

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## ABSTRACT

*Objective:* Evaluate type 2 diabetes (T2D) susceptibility variants identified from genome-wide association (GWA) 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 T2D-associated SNPs were genotyped in 1268 Hispanic- and 581 African-American participants from the IRAS-FS. SNPs were tested for association with quantitative measures of glucose homeostasis including: insulin sensitivity ( $S_I$ ), acute insulin response (AIR) and disposition index (DI).

*Results:* Previously identified risk variants in cyclin-dependent kinase 5 regulatory subunit associated protein 1-like 1 (*CDKALI*) 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 *SLC30A8* locus were nominally associated with decreased DI ( $P < 0.078$ ). Risk variants in the insulin-like growth factor 2 mRNA-binding protein 2 (*IGF2BP2*) locus were associated with a decreased DI ( $P = 0.011$ ) 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 *CDKALI*, *SLC30A8*, *IGF2BP2* and *LOC387761* is specifically mediated through defects in insulin secretion. The mechanisms of other predisposing genes remain to be elucidated.

**T**ype 2 Diabetes (T2D) is a complex disease whose pathophysiology can be characterized by peripheral insulin resistance and reduced insulin secretion. T2D is a heritable disease (1), with multiple variants conferring modest risk to its polygenic inheritance (2). Prior investigations of the genetic determinants of T2D 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 T2D risk have been elucidated. Recently, four T2D GWA studies have been reported (3-6). Taken together, these studies have identified 11 novel loci for involvement in T2D-susceptibility in European-derived populations. Of these 11 loci, eight have been replicated across studies.

The purpose of this study was to evaluate variants within the 11 novel T2D-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 T2D-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.

## **RESEARCH DESIGN AND METHODS**

**Recruitment.** Study design, recruitment and phenotyping for IRAS-FS have been described in detail (7). Briefly, the IRAS-FS is a multi-center study designed to identify the

genetic determinants of quantitative measures of glucose homeostasis. Members of large families of self-reported Hispanic ancestry ( $n=1268$  individuals in 92 pedigrees; San Antonio, TX; San Luis Valley, CO) and African Americans ( $n=581$  individuals in 42 pedigrees; Los Angeles, CA) 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 ( $S_I$ ), acute insulin response (AIR) and disposition index (DI). Distributions of the primary phenotypes are listed in Table 1.

**Genotyping.** Seventeen SNPs from 11 unique loci identified from T2D 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 two degree 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, gender, recruitment center and BMI. Adjustments for multiple comparison tests were not performed due to 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  $R^2$  was computed. The  $R^2$  statistic was calculated over just the covariates (i.e., age, gender, recruitment center, 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 T2D 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 T2D in European-derived populations (3-6).

## RESULTS

This study evaluated 1849 IRAS-FS participants, 1268 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 females and comparable age and BMI values. Compared with African Americans, Hispanic Americans were more insulin sensitive ( $S_I=2.15$  vs.  $1.63 \times 10^{-5} \text{min}^{-1}/[\text{pmol/L}]$ ;  $P=0.013$ ), had reduced insulin secretion ( $\text{AIR}=760$  vs.  $1006 \text{pmol/L}$ ;  $P<0.001$ ) and had a reduced disposition index ( $\text{DI}=1317$  vs.  $1426 \times 10^{-5} \text{min}^{-1}$ ;  $P=0.004$ ). 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 2A and compared with the results of previous genome-wide association studies from European-derived populations (3-6) in Table 3A. 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 (*CDKALI*) gene with AIR. These SNPs showed the strongest evidence of association in the dominant model (Appendix Table 1A;  $P=0.0010$  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 (Appendix 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 T2D studies of European-derived populations due to increased prevalence of the allele in T2D cases versus controls (5). Association at this locus was also seen with DI (P=0.036) following an additive model (Appendix Table 1A; P=0.011) with an increase of  $50 \times 10^{-5} \text{min}^{-1}$  (3.9%; genotype A/G) and  $353 \times 10^{-5} \text{min}^{-1}$  (27.5%; genotype G/G) in the genotypic mean for DI 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 DI (P=0.011). This SNP showed the strongest association in the additive model (Appendix Table 1A; 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 DI associated with number of the “risk” allele T. The SNPs evaluated explained, on average, less than 1% of the variance ( $R^2$ ) for the three quantitative traits examined ( $R^2$ ; Table 2A). 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 (Table 2B and Table 3B, study comparisons), the strongest evidence for association was observed

between two SNPs (rs7754840, P=0.049 and rs10946398, P=0.063) in the *CDKAL1* gene and insulin sensitivity ( $S_I$ ). These SNPs showed the strongest evidence of association in the additive model (Appendix 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  $S_I$  associated with the number of “risk” alleles C. Two additional loci showed evidence for association with DI. A nonsynonymous SNP, rs13266634 (P=0.050), in the *SLC30A8* gene was associated with DI following an additive model (Appendix Table 1B; P=0.021). The “risk” allele C was associated with a  $1011 \times 10^{-5} \text{min}^{-1}$  (38.9%; genotype T/C) and  $1236 \times 10^{-5} \text{min}^{-1}$  (47.5%; genotype C/C) decrease in DI associated with the number of “risk” alleles. SNP rs7923837, downstream of the insulin-degrading enzyme/kinesin family member 11/hematopoietically expressed homeobox (*IDE/KIF11/HHEX*) gene cluster, was modestly associated with DI (P=0.045) following an additive model (Appendix 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 DI associated with the number of risk alleles. The SNPs evaluated explained, on average, less than 1% of the variance ( $R^2$ ) for the three quantitative traits examined ( $R^2$ ; Table 2B). Analysis of SNPs in the other eight genes, *PKN2*, *IGF2BP2*, *FLJ39370*, *CDKN2B/CDKN2A*, *LOC387761*, and 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 (Table 2A and 2B). 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 for these SNPs (C allele; 0.63 versus 0.34 in Hispanic Americans) and associations at this locus were limited to nominal association with insulin sensitivity ( $P<0.063$ ). Genotypic means associated with the “risk” allele C had a decreased insulin sensitivity 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  $S_I$  and AIR as seen in Table 1. Results of this association could also reflect pleiotropy however, the genetic correlation between  $S_I$  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 DI ( $P=0.036$ ). These traits are mathematically related ( $DI=S_I \times AIR$ ) 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  $S_I$  ( $P=0.068$ ) corresponding to the “risk” allele. The confounding associations observed at the *CDKALI* and *LOC387761* loci could be

attributed partially to the dramatic difference in minor allele frequency 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  $S_I$  ( $P=0.013$ ) 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  $S_I$  could be attributed to an already increased baseline AIR.

At the solute carrier family 30, member 8 locus, a nonsynonymous variant (R325W; rs13266634) was associated with variation in the disposition index in the African American ( $P=0.050$ ) 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 DI ( $P=0.05$ ) 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 insulin-like growth factor 2 mRNA-binding protein 2 (*IGF2BP2*) locus was limited to the Hispanic American cohort. SNP rs4402960 was associated with alteration of the DI with the “risk” allele T, as determined from the GWA reports (3-6), at a comparable frequency as

compared with estimates from the European derived populations and associated with reduced DI ( $P=0.011$ ) 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 LD 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 DI ( $P=0.045$ ) exclusively in the African American population. Proposed susceptibility variants in *PKN2*, *FLJ39370*, *CDKN2A/CDKN2B*, an intragenic 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.

While the IRAS-FS was designed to study quantitative traits related to glucose homeostasis (7), there were additional subjects with T2D in these families which allowed us to perform association analysis of the 17 GWA SNPs with T2D as a qualitative trait. Likely reflecting the relatively modest numbers of T2D affecteds in IRAS-FS (181 Hispanic Americans and 71 African Americans), results were inconsistent and largely nonsignificant (Appendix Tables 2A and 2B). In Hispanic Americans, a single SNP (rs9300039) in an intragenic region on chromosome 11 was found to be associated with T2D ( $P=0.039$ ; Appendix Table 2A). The A allele of SNP rs9300039 had an odds ratio of 0.49 (95% CI: 0.25-0.96) and therefore was found to be associated with protection from T2D. Scott et al. (4) found association of the C allele with T2D “risk”,  $OR=1.48$  (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 T2D as a qualitative trait ( $P=0.021$ ; Appendix Table 2B). The T allele of SNP rs4402960 was associated with protection from T2D,  $OR=0.59$  (0.38-0.92). This finding is inconsistent with three GWA publications (3; 4; 6) which found this allele to be associated with T2D “risk” (meta analysis  $OR=1.14$ ). The difference in directionality of association could be due to a marked difference in minor allele frequency between African American ( $MAF=0.50$ ) and European-derived ( $MAF=0.30$ ) populations, which is consistent with HapMap estimates of allele frequency and LD structural differences. As noted above, there is modest power given the sample size (Appendix Table 3), nominal P-values, and limited evidence that these SNPs contribute to differential T2D risk in an independent African-American T2D case/control sample (J. Lewis, personal communication). These results suggest these T2D 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 T2D-susceptibility may influence glucose metabolism. This, taken together with the recruitment of multi-generational pedigrees, with attendant significant increase in power over a sib pair study design, enhance the ability of IRAS-FS to detect and comprehensively evaluate genes related to glucose homeostasis and in turn, T2D. Taken together, the results of the association analyses reported here suggest that a small number of T2D-susceptibility loci,

*CDKALI*, *LOC387761*, *SLC30A8* and *IGF2BP2*, identified from studies in European-derived T2D 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 the *CDKALI*, *LOC387761*, *SLC30A8* and *IGF2BP2* loci are contributing to diabetes susceptibility primarily through effects on insulin secretion as measured by acute insulin response or

through homeostatic regulation of the balance of insulin secretion and insulin sensitivity. What is strikingly absent is any strong evidence for association with insulin sensitivity, a primary component of diabetes susceptibility. Therefore, further research for genes effecting insulin sensitivity is in order.

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

	Hispanic Americans			African Americans		
	n	Mean $\pm$ SD	Median	n	Mean $\pm$ SD	Median
Subjects	1268			581		
Demographics						
Age (years)	1268	42.8 $\pm$ 14.6	41.3	581	42.9 $\pm$ 14.0	41.5
Female Gender (%)	746	58.8 %		344	59.2 %	
BMI (kg/m <sup>2</sup> )	1258	28.9 $\pm$ 6.1	28.1	576	30.0 $\pm$ 6.8	29.0
Diabetes	181	14.2%		71	12.1%	
Glucose Homeostasis						
S <sub>I</sub> (x10 <sup>-5</sup> min <sup>-1</sup> /[pmol/L])	1040	2.15 $\pm$ 1.86	1.7	500	1.63 $\pm$ 1.17	1.41
AIR (pmol/L)	1040	760.2 $\pm$ 649.3	587.0	499	1005.7 $\pm$ 826.2	771.5
DI (S <sub>I</sub> x AIR; x10 <sup>-5</sup> min <sup>-1</sup> )	1040	1316.5 $\pm$ 1236.012	1005.2	499	1425.7 $\pm$ 1269.2	1151.5
Fasting Glucose (mg/dL)	1101	93.4 $\pm$ 9.5	92.0	513	94.7 $\pm$ 9.7	93.0

TABLE 2A. Quantitative trait analysis using the 2 degree of freedom test for T2D susceptibility loci with glucose homeostasis phenotypes in the IRAS-FS Hispanic American cohort.

Phenotype	Gene	SNP	Alleles <sup>a</sup>	MAF <sup>b</sup>	Genotypic Means $\pm$ SD (n)			P-Value	R <sup>2</sup> <sup>c</sup>
					1/1	1/2	2/2		
<i>Insulin Sensitivity</i>									
	PKN2	rs6698181	C/T	0.41	2.00 $\pm$ 1.69 (371)	2.21 $\pm$ 1.94 (469)	2.33 $\pm$ 2.02 (149)	0.98	0.0001
	IGFBP2	rs4402960	G/T	0.28	2.29 $\pm$ 1.97 (539)	2.01 $\pm$ 1.77 (382)	1.81 $\pm$ 1.29 (72)	0.21	0.0040
	FLJ39370	rs17044137	T/A	0.19	2.13 $\pm$ 1.83 (661)	2.15 $\pm$ 1.85 (292)	2.88 $\pm$ 2.43 (41)	0.81	0.0004
	CDKAL1	rs7754840	G/C	0.34	2.07 $\pm$ 1.77 (467)	2.20 $\pm$ 1.89 (432)	2.43 $\pm$ 2.27 (92)	0.13	0.0014
		rs10946398	A/C	0.34	2.08 $\pm$ 1.77 (470)	2.19 $\pm$ 1.87 (438)	2.43 $\pm$ 2.27 (92)	0.14	0.0014
	SLC30A8	rs13266634	C/T	0.25	2.12 $\pm$ 1.82 (590)	2.18 $\pm$ 1.90 (370)	2.36 $\pm$ 2.14 (46)	0.84	0.0002
	CDKN2A/2B	rs10811661	T/C	0.12	2.18 $\pm$ 1.91 (774)	2.10 $\pm$ 1.72 (213)	1.70 $\pm$ 1.08 (8)	1.00	0.0002
		rs564398	T/C	0.19	2.24 $\pm$ 1.86 (675)	1.99 $\pm$ 1.85 (291)	1.78 $\pm$ 2.07 (28)	0.81	0.0004
	IDE/KIF11/HHEX	rs1111875	C/T	0.35	2.18 $\pm$ 1.83 (479)	2.17 $\pm$ 1.94 (445)	2.06 $\pm$ 1.66 (91)	0.42	0.0000
		rs5015480	T/C	0.46	2.10 $\pm$ 1.90 (245)	2.23 $\pm$ 1.91 (497)	2.08 $\pm$ 1.76 (248)	0.12	0.0029
		rs7923837	G/A	0.43	2.06 $\pm$ 1.84 (344)	2.22 $\pm$ 1.86 (492)	2.17 $\pm$ 1.95 (159)	0.39	0.0017
	LOC387761	rs7480010	A/G	0.28	2.24 $\pm$ 1.85 (551)	2.03 $\pm$ 1.89 (356)	2.26 $\pm$ 1.90 (78)	0.99	0.0004
	Intragenic	rs9300039	C/A	0.09	2.22 $\pm$ 1.92 (874)	1.72 $\pm$ 1.44 (116)	1.92 $\pm$ 0.59 (8)	0.10	0.0032
	EXT2/ALX4	rs3740878	T/C	0.43	2.09 $\pm$ 1.70 (337)	2.16 $\pm$ 1.97 (506)	2.25 $\pm$ 1.88 (149)	0.95	0.0000
		rs11037909	T/C	0.43	2.10 $\pm$ 1.69 (339)	2.16 $\pm$ 1.97 (495)	2.27 $\pm$ 1.89 (149)	0.92	0.0000
		rs1113132	G/C	0.43	2.09 $\pm$ 1.70 (338)	2.17 $\pm$ 1.98 (503)	2.26 $\pm$ 1.89 (147)	0.96	0.0000
	FTO	rs8050136	C/A	0.23	2.18 $\pm$ 1.86 (586)	2.09 $\pm$ 1.80 (346)	2.35 $\pm$ 2.34 (58)	0.40	0.0000
<i>Acute Insulin Response</i>									
	PKN2	rs6698181	C/T	0.41	719 $\pm$ 587 (371)	776 $\pm$ 685 (469)	849 $\pm$ 701 (149)	0.63	0.0005
	IGFBP2	rs4402960	G/T	0.28	780 $\pm$ 678 (539)	763 $\pm$ 678 (382)	696 $\pm$ 620 (72)	0.46	0.0039
	FLJ39370	rs17044137	T/A	0.19	795 $\pm$ 679 (661)	718 $\pm$ 611 (292)	573 $\pm$ 407 (41)	0.14	0.0040
	CDKAL1	rs7754840	G/C	0.34	834 $\pm$ 701 (467)	719 $\pm$ 590 (432)	649 $\pm$ 644 (92)	<b>0.0043</b>	0.0123
		rs10946398	A/C	0.34	836 $\pm$ 709 (470)	719 $\pm$ 588 (438)	649 $\pm$ 644 (92)	<b>0.0046</b>	0.0123
	SLC30A8	rs13266634	C/T	0.25	721 $\pm$ 599 (590)	827 $\pm$ 710 (370)	874 $\pm$ 815 (46)	0.084	0.0056
	CDKN2A/2B	rs10811661	T/C	0.12	759 $\pm$ 639 (774)	777 $\pm$ 697 (213)	1035 $\pm$ 576 (8)	0.60	0.0000
		rs564398	T/C	0.19	759 $\pm$ 632 (675)	785 $\pm$ 681 (291)	764 $\pm$ 816 (28)	0.47	0.0004
	IDE/KIF11/HHEX	rs1111875	C/T	0.35	733 $\pm$ 654 (479)	796 $\pm$ 659 (445)	715 $\pm$ 571 (91)	0.77	0.0000
		rs5015480	T/C	0.46	812 $\pm$ 624 (245)	754 $\pm$ 673 (497)	730 $\pm$ 640 (248)	0.40	0.0000
		rs7923837	G/A	0.43	773 $\pm$ 670 (344)	743 $\pm$ 650 (492)	829 $\pm$ 618 (159)	0.15	0.0000
	LOC387761	rs7480010	A/G	0.28	703 $\pm$ 610 (551)	803 $\pm$ 647 (356)	1010 $\pm$ 842 (78)	<b>0.0046</b>	0.0196
	Intragenic	rs9300039	C/A	0.09	749 $\pm$ 628 (874)	894 $\pm$ 807 (116)	599 $\pm$ 315 (8)	0.65	0.0012
	EXT2/ALX4	rs3740878	T/C	0.43	720 $\pm$ 583 (337)	817 $\pm$ 707 (506)	709 $\pm$ 592 (149)	0.11	0.0002
		rs11037909	T/C	0.43	721 $\pm$ 582 (339)	816 $\pm$ 713 (495)	706 $\pm$ 593 (149)	0.12	0.0001
		rs1113132	G/C	0.43	721 $\pm$ 583 (338)	819 $\pm$ 714 (503)	694 $\pm$ 568 (147)	0.10	0.0002
	FTO	rs8050136	C/A	0.23	755 $\pm$ 614 (586)	811 $\pm$ 740 (346)	311 $\pm$ 408 (58)	0.26	0.0002
<i>Disposition Index</i>									
	PKN2	rs6698181	C/T	0.41	1202 $\pm$ 1137 (371)	1313 $\pm$ 1168 (469)	1624 $\pm$ 1605 (149)	0.42	0.0007
	IGFBP2	rs4402960	G/T	0.28	1441 $\pm$ 1280 (539)	1220 $\pm$ 1225 (382)	1058 $\pm$ 1006 (72)	<b>0.011</b>	0.0128
	FLJ39370	rs17044137	T/A	0.19	1364 $\pm$ 1263 (661)	1199 $\pm$ 1028 (292)	1668 $\pm$ 2068 (41)	0.094	0.0015
	CDKAL1	rs7754840	G/C	0.34	1339 $\pm$ 1234 (467)	1302 $\pm$ 1182 (432)	1429 $\pm$ 1561 (92)	0.22	0.0003
		rs10946398	A/C	0.34	1342 $\pm$ 1241 (470)	1300 $\pm$ 1181 (438)	1429 $\pm$ 1561 (92)	0.21	0.0003
	SLC30A8	rs13266634	C/T	0.25	1240 $\pm$ 1177 (590)	1446 $\pm$ 1293 (370)	1529 $\pm$ 1607 (46)	0.078	0.0054
	CDKN2A/2B	rs10811661	T/C	0.12	1348 $\pm$ 1303 (774)	1262 $\pm$ 1035 (213)	1439 $\pm$ 689 (8)	0.55	0.0007
		rs564398	T/C	0.19	1404 $\pm$ 1328 (675)	1187 $\pm$ 1032 (291)	1023 $\pm$ 1072 (28)	0.93	0.0017
	IDE/KIF11/HHEX	rs1111875	C/T	0.35	1299 $\pm$ 1288 (479)	1381 $\pm$ 1221 (445)	1226 $\pm$ 1091 (91)	0.26	0.0000
		rs5015480	T/C	0.46	1361 $\pm$ 1176 (245)	1344 $\pm$ 1296 (497)	1243 $\pm$ 1198 (248)	0.21	0.0028
		rs7923837	G/A	0.43	1274 $\pm$ 1190 (344)	1327 $\pm$ 1276 (492)	1453 $\pm$ 1272 (159)	0.11	0.0014
	LOC387761	rs7480010	A/G	0.28	1284 $\pm$ 1220 (551)	1334 $\pm$ 1225 (356)	1637 $\pm$ 1443 (78)	<b>0.036</b>	0.0076
	Intragenic	rs9300039	C/A	0.09	1330 $\pm$ 1246 (874)	1316 $\pm$ 1220 (116)	1045 $\pm$ 427 (8)	0.40	0.0000
	EXT2/ALX4	rs3740878	T/C	0.43	1288 $\pm$ 1189 (337)	1374 $\pm$ 1308 (506)	1260 $\pm$ 1118 (149)	0.54	0.0000
		rs11037909	T/C	0.43	1289 $\pm$ 1186 (339)	1370 $\pm$ 1316 (495)	1257 $\pm$ 1117 (149)	0.57	0.0000
		rs1113132	G/C	0.43	1288 $\pm$ 1188 (338)	1380 $\pm$ 1314 (503)	1240 $\pm$ 1107 (147)	0.48	0.0000
	FTO	rs8050136	C/A	0.23	1362 $\pm$ 1286 (586)	1296 $\pm$ 1199 (346)	1223 $\pm$ 1139 (58)	0.99	0.0000

<sup>a</sup>Major/Minor alleles determined from the maximal set of unrelateds (n=229). Risk allele, identified from previous studies (3-6), is underlined.

<sup>b</sup>MAF; Minor Allele Frequency

<sup>c</sup>Variance proportion over baseline of the quantitative trait explained by inclusion of the SNP in the model.

**TABLE 2B.** Quantitative trait analysis using the 2 degree of freedom test for T2D-susceptibility loci with glucose homeostasis phenotypes in the IRAS-FS African American cohort.

Phenotype	Gene	SNP	Alleles <sup>a</sup>	MAF <sup>b</sup>	Genotypic Means $\pm$ SD (n)			P-Value	R <sup>2</sup> <sup>c</sup>
					1/1	1/2	2/2		
<i>Insulin Sensitivity</i>									
	PKN2	rs6698181	C/T	0.19	1.63 $\pm$ 1.22 (333)	1.71 $\pm$ 1.16 (108)	1.21 $\pm$ 0.68 (16)	0.52	0.0000
	IGFBP2	rs4402960	G/T	0.50	1.60 $\pm$ 1.23 (103)	1.65 $\pm$ 1.10 (231)	1.62 $\pm$ 1.27 (124)	0.86	0.0000
	FLJ39370	rs17044137	T/A	0.40	1.59 $\pm$ 1.07 (200)	1.63 $\pm$ 1.27 (200)	1.76 $\pm$ 1.22 (62)	0.43	0.0001
	CDKAL1	rs7754840	C/G	0.37	1.52 $\pm$ 1.06 (148)	1.62 $\pm$ 1.13 (228)	1.85 $\pm$ 1.41 (82)	<b>0.049</b>	0.0062
		rs10946398	C/A	0.38	1.54 $\pm$ 1.10 (148)	1.61 $\pm$ 1.13 (231)	1.86 $\pm$ 1.41 (81)	0.063	0.0067
	SLC30A8	rs13266634	C/T	0.11	1.59 $\pm$ 1.12 (366)	1.80 $\pm$ 1.44 (93)	1.98 $\pm$ 1.14 (6)	0.43	0.0021
	CDKN2A/2B	rs10811661	T/C	0.09	1.59 $\pm$ 1.16 (395)	1.86 $\pm$ 1.17 (62)	2.40 $\pm$ 2.36 (4)	0.50	0.0025
		rs564398	T/C	0.07	1.64 $\pm$ 1.22 (383)	1.60 $\pm$ 1.04 (81)	1.58 $\pm$ 0.00 (1)	0.94	0.0000
	IDE/KIF11/HHEX	rs1111875	C/T	0.22	1.60 $\pm$ 1.12 (282)	1.63 $\pm$ 1.17 (176)	1.85 $\pm$ 1.51 (29)	0.44	0.0001
		rs5015480	C/T	0.34	1.63 $\pm$ 1.16 (161)	1.62 $\pm$ 1.16 (217)	1.63 $\pm$ 1.28 (79)	0.88	0.0000
		rs7923837	G/A	0.06	1.64 $\pm$ 1.16 (395)	1.64 $\pm$ 1.36 (66)	1.26 $\pm$ 1.42 (4)	0.61	0.0001
	LOC387761	rs7480010	G/A	0.17	1.54 $\pm$ 1.15 (342)	1.84 $\pm$ 1.23 (111)	2.35 $\pm$ 0.92 (7)	0.07	0.0092
	Intragenic	rs9300039	C/A	0.18	1.69 $\pm$ 1.22 (348)	1.49 $\pm$ 1.07 (96)	1.50 $\pm$ 1.24 (11)	0.37	0.0045
	EXT2/ALX4	rs3740878	T/C	0.13	1.61 $\pm$ 1.20 (370)	1.72 $\pm$ 1.07 (89)	0.98 $\pm$ 0.33 (3)	0.86	0.0000
		rs11037909	T/C	0.17	1.60 $\pm$ 1.19 (334)	1.75 $\pm$ 1.20 (112)	1.48 $\pm$ 0.62 (12)	0.57	0.0000
		rs1113132	G/C	0.12	1.62 $\pm$ 1.21 (376)	1.68 $\pm$ 1.07 (83)	0.98 $\pm$ 0.33 (3)	0.92	0.0008
	FTO	rs8050136	A/C	0.49	1.72 $\pm$ 1.14 (105)	1.58 $\pm$ 1.16 (221)	1.67 $\pm$ 1.25 (135)	0.11	0.0070
<i>Acute Insulin Response</i>									
	PKN2	rs6698181			985 $\pm$ 832 (332)	1040 $\pm$ 883 (108)	1032 $\pm$ 841 (16)	0.93	0.0000
	IGFBP2	rs4402960	G/T	0.50	1056 $\pm$ 884 (103)	982 $\pm$ 830 (230)	1007 $\pm$ 849 (124)	0.87	0.0001
	FLJ39370	rs17044137	T/A	0.40	1047 $\pm$ 810 (200)	1008 $\pm$ 907 (200)	893 $\pm$ 739 (61)	0.38	0.0010
	CDKAL1	rs7754840	C/G	0.37	1011 $\pm$ 769 (147)	1063 $\pm$ 903 (228)	823 $\pm$ 745 (82)	0.14	0.0055
		rs10946398	C/A	0.38	1011 $\pm$ 769 (147)	1064 $\pm$ 915 (231)	828 $\pm$ 749 (81)	0.15	0.0054
	SLC30A8	rs13266634	C/T	0.11	1014 $\pm$ 872 (365)	962 $\pm$ 720 (93)	1198 $\pm$ 892 (6)	0.81	0.0003
	CDKN2A/2B	rs10811661	T/C	0.09	1011 $\pm$ 870 (394)	991 $\pm$ 698 (62)	733 $\pm$ 583 (4)	0.99	0.0001
		rs564398	T/C	0.07	1020 $\pm$ 858 (382)	831 $\pm$ 777 (81)	1041 $\pm$ 0 (1)	0.91	0.0052
	IDE/KIF11/HHEX	rs1111875	C/T	0.22	1106 $\pm$ 902 (282)	877 $\pm$ 643 (175)	970 $\pm$ 1032 (29)	0.12	0.0155
		rs5015480	C/T	0.34	1019 $\pm$ 896 (160)	981 $\pm$ 788 (217)	1063 $\pm$ 906 (79)	0.34	0.0000
		rs7923837	G/A	0.06	1027 $\pm$ 851 (394)	903 $\pm$ 809 (66)	444 $\pm$ 326 (4)	0.063	0.0178
	LOC387761	rs7480010	G/A	0.17	1037 $\pm$ 838 (341)	944 $\pm$ 889 (111)	571 $\pm$ 278 (7)	0.33	0.0044
	Intragenic	rs9300039	C/A	0.18	991 $\pm$ 813 (347)	1037 $\pm$ 944 (96)	1251 $\pm$ 1062 (11)	0.28	0.0035
	EXT2/ALX4	rs3740878	T/C	0.13	1008 $\pm$ 837 (369)	1007 $\pm$ 894 (89)	1087 $\pm$ 378 (3)	0.88	0.0004
		rs11037909	T/C	0.17	1010 $\pm$ 851 (333)	966 $\pm$ 836 (112)	1196 $\pm$ 929 (12)	0.70	0.0008
		rs1113132	G/C	0.12	999 $\pm$ 834 (375)	1040 $\pm$ 912 (83)	1087 $\pm$ 378 (3)	0.66	0.0002
	FTO	rs8050136	A/C	0.49	1052 $\pm$ 865 (105)	1025 $\pm$ 858 (220)	937 $\pm$ 814 (135)	0.53	0.0011
<i>Disposition Index</i>									
	PKN2	rs6698181			1378 $\pm$ 1292 (332)	1497 $\pm$ 1250 (108)	1329 $\pm$ 1094 (16)	0.75	0.0009
	IGFBP2	rs4402960	G/T	0.50	1584 $\pm$ 1645 (103)	1347 $\pm$ 1102 (230)	1415 $\pm$ 1272 (124)	0.80	0.0001
	FLJ39370	rs17044137	T/A	0.40	1471 $\pm$ 1244 (200)	1342 $\pm$ 1212 (200)	1540 $\pm$ 1655 (61)	0.25	0.0000
	CDKAL1	rs7754840	C/G	0.37	1382 $\pm$ 1190 (147)	1478 $\pm$ 1347 (228)	1325 $\pm$ 1316 (82)	0.44	0.0000
		rs10946398	C/A	0.38	1384 $\pm$ 1185 (147)	1466 $\pm$ 1338 (231)	1338 $\pm$ 1319 (81)	0.54	0.0000
	SLC30A8	rs13266634	C/T	0.11	1364 $\pm$ 1203 (365)	1589 $\pm$ 1491 (93)	2600 $\pm$ 2276 (6)	<b>0.050</b>	0.0032
	CDKN2A/2B	rs10811661	T/C	0.09	1402 $\pm$ 1308 (394)	1511 $\pm$ 1120 (62)	1237 $\pm$ 711 (4)	0.87	0.0011
		rs564398	T/C	0.07	1439 $\pm$ 1334 (382)	1326 $\pm$ 1042 (81)	1645 $\pm$ 0 (1)	0.97	0.0023
	IDE/KIF11/HHEX	rs1111875	C/T	0.22	1524 $\pm$ 1397 (282)	1310 $\pm$ 1083 (175)	1346 $\pm$ 1113 (29)	0.094	0.0067
		rs5015480	C/T	0.34	1359 $\pm$ 1244 (160)	1436 $\pm$ 1337 (217)	1495 $\pm$ 1259 (79)	0.21	0.0009
		rs7923837	G/A	0.06	1448 $\pm$ 1297 (394)	1289 $\pm$ 1223 (66)	784 $\pm$ 1116 (4)	<b>0.045</b>	0.0100
	LOC387761	rs7480010	G/A	0.17	1366 $\pm$ 1273 (341)	1558 $\pm$ 1324 (111)	1243 $\pm$ 554 (7)	0.56	0.0016
	Intragenic	rs9300039	C/A	0.18	1484 $\pm$ 1361 (347)	1255 $\pm$ 1061 (96)	1417 $\pm$ 1184 (11)	0.71	0.0011
	EXT2/ALX4	rs3740878	T/C	0.13	1411 $\pm$ 1316 (369)	1458 $\pm$ 1151 (89)	1017 $\pm$ 385 (3)	0.74	0.0001
		rs11037909	T/C	0.17	1408 $\pm$ 1335 (333)	1382 $\pm$ 1093 (112)	1679 $\pm$ 1356 (12)	0.48	0.0002
		rs1113132	G/C	0.12	1410 $\pm$ 1319 (375)	1472 $\pm$ 1170 (83)	1017 $\pm$ 385 (3)	0.66	0.0006
	FTO	rs8050136	A/C	0.49	1534 $\pm$ 1299 (105)	1369 $\pm$ 1152 (220)	1420 $\pm$ 1482 (135)	0.16	0.0046

<sup>a</sup>Major/Minor alleles determined from the maximal set of unrelateds (n=229). Risk allele, identified from previous studies (3-6), is underlined.

<sup>b</sup>MAF; Minor Allele Frequency

<sup>c</sup>Variance proportion over baseline of the quantitative trait explained by inclusion of the SNP in the model.

**Table 3A.** 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							
SNP	Risk		OR <sup>2</sup>	OR (95% CI) <sup>3</sup>	OR (95% CI) <sup>4</sup>	OR (95% CI) <sup>5</sup>	Minor		Trait	P-Value	Genotypic Means		
	Allele	Frequency <sup>1</sup>					Allele	Frequency			2df	1/1	1/2
<i>Insulin-like Growth Factor 2 mRNA-binding protein 2 (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	0.28	S <sub>I</sub>	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)
									DI	<b>0.011</b>	1441 ± 1280 (539)	1220 ± 1225 (382)	1058 ± 1006 (72)
<i>Cyclin-dependent Kinase 5 Regulatory Subunit Associated Protein 1-like 1 (CDKAL1)</i>													
rs7754840	C	0.31		1.08 (1.03-1.14)	1.12 (1.03-1.22)		C	0.34	S <sub>I</sub>	0.13	2.07 ± 1.77 (467)	2.20 ± 1.89 (432)	2.43 ± 2.27 (92)
									AIR	<b>0.0043</b>	834 ± 701 (467)	719 ± 590 (432)	649 ± 644 (92)
									DI	0.22	1339 ± 1234 (467)	1302 ± 1182 (432)	1429 ± 1561 (92)
rs10946398	C	0.31				1.16 (1.10-1.22)	C	0.34	S <sub>I</sub>	0.14	2.08 ± 1.77 (470)	2.19 ± 1.87 (438)	2.43 ± 2.27 (92)
									AIR	<b>0.0046</b>	836 ± 709 (470)	719 ± 588 (438)	649 ± 644 (92)
									DI	0.21	1342 ± 1241 (470)	1300 ± 1181 (438)	1429 ± 1561 (92)
<i>Hypothetical Gene (LOC387761)</i>													
rs7480010	G	0.25	1.40 ± 0.25		1.03		G	0.28	S <sub>I</sub>	0.99	2.24 ± 1.85 (551)	2.03 ± 1.89 (356)	2.26 ± 1.90 (78)
									AIR	<b>0.0046</b>	703 ± 610 (551)	803 ± 647 (356)	1010 ± 842 (78)
									DI	<b>0.036</b>	1284 ± 1220 (551)	1334 ± 1225 (356)	1637 ± 1443 (78)

<sup>1</sup> Hapmap CEU minor allele frequencies

<sup>2</sup> Sladek et al. A genome-wide association study identifies novel risk loci for type 2 diabetes. (5) (*n*=2617 Cases/2894 Controls)

<sup>3</sup> Saxena et al. Genome-Wide Association Analysis Identifies Loci for Type 2 Diabetes and Triglyceride Levels. (3) (*n*=6529 Cases/7252 Controls)

<sup>4</sup> Scott et al. A Genome-Wide Association Study of Type 2 Diabetes in Finns Detects Multiple Susceptibility Variants. (4) (*n*=2376 Cases/2432 Controls)

<sup>5</sup> Zeggini et al. Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. (6) (*n*=5681 Cases/8284 Control)

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

Previously Published GWA Studies							IRAS-FS African Americans						
SNP	Risk		OR <sup>2</sup>	OR (95% CI) <sup>3</sup>	OR (95% CI) <sup>4</sup>	OR (95% CI) <sup>5</sup>	Minor		Trait	P-Value	Genotypic Means		
	Allele	Frequency <sup>1</sup>					Allele	Frequency			2df	1/1	1/2
<i>Cyclin-dependent Kinase 5 Regulatory Subunit Associated Protein 1-like 1 (CDKALI)</i>													
rs7754840	C	0.31		1.08 (1.03-1.14)	1.12 (1.03-1.22)		G	0.37	S <sub>I</sub>	<b>0.049</b>	1.52 ± 1.06 (148)	1.62 ± 1.13 (228)	1.85 ± 1.41 (82)
									AIR	0.14	1011 ± 769 (147)	1063 ± 903 (228)	823 ± 745 (82)
									DI	0.44	1382 ± 1190 (147)	1478 ± 1347 (228)	1325 ± 1316 (82)
rs10946398	C	0.31			1.16 (1.10-1.22)		A	0.38	S <sub>I</sub>	0.063	1.54 ± 1.10 (148)	1.61 ± 1.13 (231)	1.86 ± 1.41 (81)
									AIR	0.15	1011 ± 769 (147)	1064 ± 915 (231)	828 ± 749 (81)
									DI	0.54	1384 ± 1185 (147)	1466 ± 1338 (231)	1338 ± 1319 (81)
<i>Solute Carrier Family 30, Member 8 (SLC30A8)</i>													
rs13266634	C	0.75	1.53 ± 0.31	1.07 (1.00-1.16)	1.18 (1.09-1.29)	1.12 (1.05-1.18)	T	0.11	S <sub>I</sub>	0.43	1.59 ± 1.12 (366)	1.80 ± 1.44 (93)	1.98 ± 1.14 (6)
									AIR	0.81	1014 ± 872 (365)	962 ± 720 (93)	1198 ± 892 (6)
									DI	<b>0.050</b>	1364 ± 1203 (365)	1589 ± 1491 (93)	2600 ± 2276 (6)
<i>Insulin-degrading Enzyme (IDE) / Kinesin Family Member 11 (KIF11) / Hematopoietically Expressed Homeobox (HHEX)</i>													
rs1111875	C	0.56	1.44 ± 0.24	1.14 (1.06-1.22)	1.10 (1.01-1.19)	1.08 (1.01-1.15)	T	0.22	S <sub>I</sub>	0.44	1.60 ± 1.12 (282)	1.63 ± 1.17 (176)	1.85 ± 1.51 (29)
									AIR	0.12	1106 ± 902 (282)	877 ± 643 (175)	970 ± 1032 (29)
									DI	0.094	1524 ± 1397 (282)	1310 ± 1083 (175)	1346 ± 1113 (29)
rs5015480	C	0.45			1.13 (1.07-1.19)		T	0.34	S <sub>I</sub>	0.88	1.63 ± 1.16 (161)	1.62 ± 1.16 (217)	1.63 ± 1.28 (79)
									AIR	0.34	1019 ± 896 (160)	981 ± 788 (217)	1063 ± 906 (79)
									DI	0.21	1359 ± 1244 (160)	1436 ± 1337 (217)	1495 ± 1259 (79)
rs7923837	A	0.37	1.45 ± 0.25				A	0.06	S <sub>I</sub>	0.61	1.64 ± 1.16 (395)	1.64 ± 1.36 (66)	1.26 ± 1.42 (4)
									AIR	0.063	1027 ± 851 (394)	903 ± 809 (66)	444 ± 326 (4)
									DI	<b>0.045</b>	1448 ± 1297 (394)	1289 ± 1223 (66)	784 ± 1116 (4)

<sup>1</sup> Hapmap CEU minor allele frequencies

<sup>2</sup> Sladek et al. A genome-wide association study identifies novel risk loci for type 2 diabetes. (5) (*n*=2617 Cases/2894 Controls)

<sup>3</sup> Saxena et al. Genome-Wide Association Analysis Identifies Loci for Type 2 Diabetes and Triglyceride Levels. (3) (*n*=6529 Cases/7252 Controls)

<sup>4</sup> Scott et al. A Genome-Wide Association Study of Type 2 Diabetes in Finns Detects Multiple Susceptibility Variants. (4) (*n*=2376 Cases/2432 Controls)

<sup>5</sup> Zeggini et al. Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes. (6) (*n*=5681 Cases/8284 Control)