

Association of *SSTR2* Polymorphisms and Glucose Homeostasis Phenotypes

The Insulin Resistance Atherosclerosis Family Study

Beth S. Sutton,^{1,2} Nicholette D. Palmer,^{1,2} Carl D. Langefeld,³ Bingzhong Xue,² Alexandria Proctor,^{1,2} Julie T. Ziegler,³ Steven M. Haffner,⁴ Jill M. Norris,⁵ and Donald W. Bowden^{1,2,6}

OBJECTIVE—This study evaluated the influence of somatostatin receptor type 2 (*SSTR2*) polymorphisms on measures of glucose homeostasis in the Insulin Resistance Atherosclerosis Family Study (IRASFS). *SSTR2* is a G-protein-coupled receptor that, in response to somatostatin, mediates inhibition of insulin, glucagon, and growth hormone release and thus may affect glucose homeostasis.

RESEARCH DESIGN AND METHODS—Ten single nucleotide polymorphisms (SNPs) spanning the gene were chosen using a SNP density selection algorithm and genotyped on 1,425 Hispanic-American individuals from 90 families in the IRASFS. These families comprised two samples (set 1 and set 2), which were analyzed individually and as a combined set. Single SNP tests of association were performed for four glucose homeostasis measures—insulin sensitivity (S_I), acute insulin response (AIR), disposition index (DI), and fasting blood glucose (FBG)—using generalized estimating equations.

RESULTS—The *SSTR2* locus was encompassed by a single linkage disequilibrium (LD) block ($D' = 0.91$ – 1.00 ; $r^2 = 0.09$ – 0.97) that contained four of the ten SNPs evaluated. Within the *SSTR2*-containing LD block, evidence of association was observed in each of the two sets and in a combined analysis with decreased S_I ($\beta_{\text{homozygous}} = -0.16$; $P_{\text{meta-analysis}} = 0.0024$ – 0.0030), decreased DI ($\beta_{\text{homozygous}} = -0.35$ to -5.16 ; $P_{\text{meta-analysis}} = 0.0075$ – 0.027), and increased FBG ($\beta_{\text{homozygous}} = 2.30$; $P_{\text{meta-analysis}} = 0.045$). SNPs outside the *SSTR2*-containing LD block were not associated with measures of glucose homeostasis.

CONCLUSIONS—We observed evidence for association of *SSTR2* polymorphisms with measures of glucose homeostasis. Thus, variants in *SSTR2* may influence pathways of S_I to modulate glucose homeostasis. *Diabetes* 58:1457–1462, 2009

From the ¹Department of Biochemistry, Wake Forest University School of Medicine, Winston-Salem, North Carolina; the ²Center for Human Genomics, Wake Forest University School of Medicine, Winston-Salem, North Carolina; the ³Department of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina; the ⁴Department of Medicine, University of Texas Health Sciences Center at San Antonio, San Antonio, Texas; the ⁵Department of Preventive Medicine and Biometrics, University of Colorado Denver, Denver, Colorado; and the ⁶Department of Internal Medicine, University of Texas Health Sciences Center at San Antonio, San Antonio, Texas.

Corresponding author: Donald W. Bowden, dbowden@wfubmc.edu.

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Somatostatin (SRIF) is a hormone found throughout the body that inhibits the action or expression of several hormones including insulin, glucagon, and growth hormone (1). SRIF is an important regulator of the endocrine system, exerting its effects through interactions with pituitary growth hormone, thyroid-stimulating hormone, and several hormones of the gastrointestinal tract. Five G-protein-coupled receptors (SRIF receptor type [*SSTR*] 1–5) that bind SRIF exist, each exerting differential effects based on the receptor bound and localization. *SSTR2* is found primarily in the pancreas, pituitary, and stomach (2). Several studies have evaluated the effects of SRIF on the respective receptors. Rat studies have found that *SSTR2* ligands mediate inhibition of glucagon release, whereas *SSTR5* mediates inhibition of insulin release (3). In addition, a study of pancreatic islets from *SSTR2* knockout mice supported the finding in rats, concluding that SRIF inhibition of glucagon release is primarily regulated through interaction with *SSTR2*, whereas insulin secretion is primarily regulated by *SSTR5* (4). Human studies of the pancreas revealed slightly different results, suggesting that SRIF can inhibit insulin release through the *SSTR2* receptor (5). In contrast, Cheng et al. (6) observed that *SSTR2* mediates the SRIF-induced increase in insulin secretion, although the increase was detected only in the presence of arginine vasopressin. Based on these studies, it is apparent that whereas *SSTR2* does appear to mediate the regulation of insulin and glucagon, the exact mechanism remains obscure.

To date, no studies have assessed the effects of *SSTR2* polymorphisms on glucose homeostasis traits in population-based studies. The Insulin Resistance Atherosclerosis Family Study (IRASFS) is a multicenter study investigating the genetic contributions to glucose homeostasis and adiposity and includes a population suitable for studying such effects. Previous studies in the IRASFS of *SSTR2* as a positional candidate gene for alterations in the amount of visceral adipose tissue present in study participants (7,8) revealed no association; however, the role in glucose homeostasis, as suggested by the literature, was not assessed. The IRASFS is an extensively phenotyped population with measures of glucose homeostasis derived from minimal model (MINMOD) analysis of frequently sampled intravenous glucose tolerance tests, which include insulin sensitivity (S_I), acute insulin response (AIR), and disposition index (DI) as well as fasting blood glucose (FBG). In this study, we have evaluated the influence of *SSTR2* polymorphisms on measures of glucose homeostasis with

TABLE 2
Genotypic means for quantitative measures of glucose homeostasis calculated in set 1 of the IRASFS Hispanic-American population

Phenotype	SNP	Alleles [†]	MAF	Genotypic means \pm SD (<i>n</i>)*			<i>P</i> [‡]
				1/1	1/2	2/2	
S _I	rs1037257	C/T	0.37	2.37 \pm 2.21 (207)	1.96 \pm 1.59 (280)	2.13 \pm 2.17 (85)	0.027
	rs4969076	C/G	0.22	2.13 \pm 2.01 (315)	2.05 \pm 1.69 (198)	2.24 \pm 2.21 (30)	0.98
	rs1037260	T/G	0.13	2.09 \pm 1.90 (470)	2.25 \pm 2.05 (94)	2.18 \pm 1.74 (5)	0.40
	rs11077670	G/A	0.14	2.09 \pm 1.98 (398)	2.22 \pm 1.86 (139)	2.01 \pm 2.12 (8)	0.91
	rs1868486	G/T	0.30	2.23 \pm 2.06 (254)	2.10 \pm 1.92 (232)	1.81 \pm 1.56 (73)	0.0040
	rs714925	A/G	0.30	2.19 \pm 2.03 (244)	2.07 \pm 1.89 (243)	1.76 \pm 1.45 (71)	0.011
	rs998571	A/G	0.29	2.24 \pm 2.01 (261)	2.14 \pm 1.97 (219)	1.71 \pm 1.43 (73)	0.0040
	rs7220818	A/G	0.37	1.93 \pm 1.67 (216)	2.11 \pm 1.94 (268)	2.71 \pm 2.33 (91)	0.0020
	rs6501603	T/G	0.48	2.27 \pm 2.16 (152)	2.03 \pm 1.86 (276)	2.15 \pm 1.72 (128)	0.51
	rs4969017	T/C	0.03	2.14 \pm 1.97 (529)	1.96 \pm 1.13 (20)	1.01 \pm 0.00 (1)	0.18
AIR	rs1037257	C/T	0.37	713 \pm 543 (207)	743 \pm 619 (280)	845 \pm 721 (85)	0.54
	rs4969076	C/G	0.22	788 \pm 623 (315)	698 \pm 585 (198)	820 \pm 627 (30)	0.29
	rs1037260	T/G	0.13	763 \pm 644 (470)	761 \pm 566 (94)	513 \pm 177 (5)	0.69
	rs11077670	G/A	0.14	770 \pm 620 (398)	676 \pm 698 (139)	920 \pm 737 (8)	0.17
	rs1868486	G/T	0.30	727 \pm 532 (254)	801 \pm 706 (232)	755 \pm 696 (73)	0.80
	rs714925	A/G	0.30	728 \pm 532 (244)	800 \pm 699 (243)	751 \pm 708 (71)	0.81
	rs998571	A/G	0.29	722 \pm 525 (261)	812 \pm 724 (219)	774 \pm 699 (73)	0.66
	rs7220818	A/G	0.37	788 \pm 643 (216)	739 \pm 637 (268)	736 \pm 567 (91)	0.66
	rs6501603	T/G	0.48	759 \pm 584 (152)	764 \pm 650 (276)	702 \pm 581 (128)	0.72
	rs4969017	T/C	0.03	765 \pm 626 (529)	579 \pm 297 (20)	195 \pm 0 (1)	0.14
DI	rs1037257	C/T	0.37	1,375 \pm 1,279 (207)	1,225 \pm 1,201 (280)	1,390 \pm 1,345 (85)	0.053
	rs4969076	C/G	0.22	1,397 \pm 1,414 (315)	1,130 \pm 893 (198)	1,553 \pm 1,539 (30)	0.34
	rs1037260	T/G	0.13	1,273 \pm 1,229 (470)	1,485 \pm 1,409 (94)	1,207 \pm 1,052 (5)	0.62
	rs11077670	G/A	0.14	1,344 \pm 1,309 (398)	1,133 \pm 1,027 (139)	1,655 \pm 1,780 (8)	0.036
	rs1868486	G/T	0.30	1,360 \pm 1,349 (254)	1,342 \pm 1,283 (232)	1,027 \pm 939 (73)	0.0020
	rs714925	A/G	0.30	1,348 \pm 1,337 (244)	1,327 \pm 1,202 (243)	979 \pm 838 (71)	0.0010
	rs998571	A/G	0.29	1,352 \pm 1,292 (261)	1,388 \pm 1,366 (219)	994 \pm 837 (73)	0.0010
	rs7220818	A/G	0.37	1,254 \pm 1,176 (216)	1,262 \pm 1,280 (268)	1,597 \pm 1,404 (91)	0.052
	rs6501603	T/G	0.48	1,463 \pm 1,437 (152)	1,230 \pm 1,176 (276)	1,227 \pm 1,004 (128)	0.68
	rs4969017	T/C	0.03	1,328 \pm 1,293 (529)	1,100 \pm 975 (20)	197 \pm 0 (1)	0.94
FBG	rs1037257	C/T	0.37	93.28 \pm 9.35 (220)	93.85 \pm 10.25 (298)	92.88 \pm 9.68 (88)	0.62
	rs4969076	C/G	0.22	93.57 \pm 10.24 (343)	93.69 \pm 9.01 (202)	91.16 \pm 8.15 (32)	0.043
	rs1037260	T/G	0.13	93.26 \pm 9.55 (498)	94.35 \pm 10.48 (99)	94.07 \pm 11.80 (7)	0.14
	rs11077670	G/A	0.14	93.57 \pm 9.99 (427)	93.38 \pm 9.49 (144)	96.31 \pm 11.29 (8)	0.41
	rs1868486	G/T	0.30	92.49 \pm 9.70 (272)	94.62 \pm 10.02 (243)	94.24 \pm 9.35 (77)	0.019
	rs714925	A/G	0.30	92.34 \pm 9.52 (264)	94.48 \pm 10.00 (253)	94.05 \pm 9.58 (75)	0.005
	rs998571	A/G	0.29	92.41 \pm 9.48 (280)	94.24 \pm 10.27 (230)	94.23 \pm 9.32 (77)	0.014
	rs7220818	A/G	0.37	93.86 \pm 9.46 (222)	93.88 \pm 10.00 (286)	90.96 \pm 9.23 (101)	0.014
	rs6501603	T/G	0.48	93.30 \pm 9.76 (166)	94.12 \pm 10.37 (293)	92.52 \pm 8.86 (132)	0.25
	rs4969017	T/C	0.03	93.50 \pm 9.69 (562)	90.59 \pm 9.68 (22)	93.00 \pm 0.00 (1)	0.19

Boldface data indicate *P* values <0.05. *Genotypic means \pm SD (*n*) for homozygotes of the major allele (1/1) as well as heterozygotes (1/2) and homozygotes of the minor allele (2/2). [†]Major/minor alleles. [‡]Test for association among each SNP-trait combination using a series of generalized estimating equations.

To test for association among each SNP-trait combination by set and in the combined analysis, a series of generalized estimating equations (16) was computed. When necessary, quantitative traits were transformed to approximate the distributional assumptions of conditional normality (conditional on covariates) and homogeneity of variance. Familial correlations within a pedigree were adjusted for by assuming exchangeable correlation and computing the sandwich estimator of the variance (17). The sandwich estimator is also denoted the robust or empirical estimator of the variance and is a consistent estimator even under misspecification of the correlation matrix. For each SNP and phenotype, the 2 d.f. overall test of genotypic association was performed and reported. When evidence of association was observed, three individual contrasts defined by the genetic models (dominant, additive, and recessive) were computed. In addition, a meta-analysis was computed treating set 1 and set 2 as different populations. We modeled set 1 or set 2 affiliation as a random effect in a variance component-measured genotype model, as implemented in the sequential oligogenic linkage analysis (18). This standard approach to meta-analysis accounts for unknown sources of confounding affiliated with the subsamples of set 1 and set 2 (19). To test for whether the effect was consistent across the two subsamples, a test of SNP by set (dummy variable parameterization) interaction (effect heterogeneity) was computed as the centered cross product. Absence of an interaction suggests

there is no detected evidence of heterogeneity of effect across the subsamples. Tests reported here were computed adjusting for age, sex, recruitment center, and BMI. Association results reported herein were not adjusted for multiple comparisons due to inter-SNP and inter-trait correlations.

RESULTS

A total of 10 SNPs at the *SSTR2* locus were genotyped on 1,425 Hispanic individuals. The majority of SNPs in this study had an MAF >0.15. Using the Haploview Tagger program, a subset of the genotyped SNPs (six SNPs genotyped in the HapMap Build 36 dataset) captured common variation (HapMap CEU, MAF >0.05, aggressive tagging algorithm) with a mean $r^2 > 0.70$. *D'* values were high between SNPs within the *SSTR2* gene (rs11077670, rs1868486, rs714925, rs998571, and rs7220818; *D'* ≥ 0.8) and declined 5' and 3' to these markers (*D'* <0.6; Fig. 1).

TABLE 3

Genotypic means for quantitative measures of glucose homeostasis calculated in set 2 of the IRASFS Hispanic-American population

Phenotype	SNP	Alleles†	MAF	Genotypic means ± SD (n)*			P‡
				1/1	1/2	2/2	
S ₁	rs1037257	C/T	0.40	2.35 ± 1.78 (143)	2.08 ± 1.78 (218)	2.34 ± 1.91 (61)	0.60
	rs4969076	C/G	0.22	2.31 ± 1.85 (34)	2.15 ± 1.75 (162)	1.82 ± 1.53 (25)	0.15
	rs1037260	T/G	0.15	2.19 ± 1.72 (330)	2.28 ± 1.99 (92)	3.19 ± 1.55 (2)	0.83
	rs11077670	G/A	0.10	2.29 ± 1.84 (318)	1.96 ± 1.69 (88)	1.81 ± 1.57 (6)	0.039
	rs1868486	G/T	0.28	2.24 ± 1.78 (199)	2.23 ± 1.79 (191)	1.68 ± 1.72 (36)	0.038
	rs714925	A/G	0.28	2.27 ± 1.81 (196)	2.25 ± 1.79 (191)	1.69 ± 1.75 (35)	0.097
	rs998571	A/G	0.25	2.26 ± 1.79 (214)	2.21 ± 1.79 (178)	1.70 ± 1.64 (36)	0.11
	rs7220818	A/G	0.41	2.17 ± 1.72 (132)	2.20 ± 1.76 (219)	2.18 ± 1.85 (72)	0.98
	rs6501603	T/G	0.45	2.35 ± 1.79 (141)	2.11 ± 1.77 (203)	2.22 ± 1.92 (73)	0.61
	rs4969017	T/C	0.02	2.21 ± 1.79 (417)	2.00 ± 1.66 (16)		0.15
AIR	rs1037257	C/T	0.40	697 ± 629 (143)	820 ± 739 (218)	841 ± 695 (61)	0.32
	rs4969076	C/G	0.22	773 ± 664 (234)	748 ± 692 (162)	776 ± 829 (25)	0.80
	rs1037260	T/G	0.15	740 ± 681 (330)	867 ± 712 (92)	455 ± 6 (2)	0.34
	rs11077670	G/A	0.10	773 ± 641 (318)	815 ± 886 (88)	831 ± 358 (6)	0.84
	rs1868486	G/T	0.28	773 ± 676 (199)	797 ± 727 (191)	618 ± 593 (36)	0.021
	rs714925	A/G	0.28	777 ± 671 (196)	794 ± 727 (191)	629 ± 605 (35)	0.089
	rs998571	A/G	0.25	786 ± 660 (214)	777 ± 740 (178)	643 ± 596 (36)	0.26
	rs7220818	A/G	0.41	757 ± 626 (132)	789 ± 744 (219)	747 ± 646 (72)	0.86
	rs6501603	T/G	0.45	709 ± 602 (141)	781 ± 708 (203)	933 ± 837 (73)	0.66
	rs4969017	T/C	0.02	744 ± 661 (417)	1,236 ± 1,130 (16)		0.12
DI	rs1037257	C/T	0.40	1,270 ± 1,017 (151)	1,375 ± 1,245 (218)	1,520 ± 1,499 (61)	0.56
	rs4969076	C/G	0.22	1,426 ± 1,247 (234)	1,255 ± 1,152 (162)	1,122 ± 1,149 (25)	0.0050
	rs1037260	T/G	0.15	1,307 ± 1,163 (330)	1,462 ± 1,321 (92)	1,445 ± 685 (2)	0.53
	rs11077670	G/A	0.10	1,415 ± 1,236 (318)	1,143 ± 1,106 (88)	1,468 ± 1,524 (6)	0.0010
	rs1868486	G/T	0.28	1,305 ± 1,049 (199)	1,436 ± 1,311 (191)	1,035 ± 1,402 (36)	0.088
	rs714925	A/G	0.28	1,315 ± 1,032 (196)	1,430 ± 1,309 (191)	1,072 ± 1,457 (35)	0.21
	rs998571	A/G	0.25	1,380 ± 1,158 (214)	1,353 ± 1,216 (178)	1,096 ± 1,430 (36)	0.20
	rs7220818	A/G	0.41	1,443 ± 1,339 (132)	1,294 ± 1,106 (219)	1,265 ± 1,098 (72)	0.63
	rs6501603	T/G	0.45	1,312 ± 1,180 (141)	1,313 ± 1,161 (203)	1,578 ± 1,409 (73)	0.32
	rs4969017	T/C	0.02	1,323 ± 1,200 (417)	1,540 ± 1,199 (16)		0.59
FBG	rs1037257	C/T	0.40	92.68 ± 9.98 (151)	93.40 ± 9.01 (231)	93.93 ± 7.27 (63)	0.21
	rs4969076	C/G	0.22	93.31 ± 9.04 (246)	92.47 ± 9.20 (172)	97.52 ± 10.32 (26)	0.18
	rs1037260	T/G	0.15	93.43 ± 9.46 (350)	92.38 ± 7.98 (95)	90.33 ± 7.94 (3)	0.53
	rs11077670	G/A	0.10	92.75 ± 8.99 (336)	94.68 ± 9.83 (92)	97.75 ± 5.40 (6)	0.099
	rs1868486	G/T	0.28	93.43 ± 9.53 (212)	92.18 ± 8.51 (199)	97.41 ± 9.63 (39)	0.024
	rs714925	A/G	0.28	93.40 ± 9.59 (209)	92.24 ± 8.46 (199)	97.87 ± 9.44 (38)	0.030
	rs998571	A/G	0.25	93.34 ± 9.47 (229)	92.59 ± 8.55 (185)	96.25 ± 10.56 (38)	0.51
	rs7220818	A/G	0.41	93.89 ± 8.88 (143)	92.88 ± 9.09 (226)	93.29 ± 10.29 (77)	0.64
	rs6501603	T/G	0.45	93.02 ± 9.20 (147)	93.15 ± 9.01 (217)	93.91 ± 9.27 (76)	0.60
	rs4969017	T/C	0.02	93.28 ± 9.24 (438)	92.92 ± 8.70 (18)		0.92

Boldface data indicate P values < 0.05 . *Genotypic means ± SD (n) for homozygotes of the major allele (1/1) as well as heterozygotes (1/2) and homozygotes of the minor allele (2/2). †Major/minor alleles. ‡Test for association among each SNP-trait combination using a series of generalized estimating equations.

In set 1 (Table 2), the majority of the SNPs in the *SSTR2*-containing LD block ($D' > 0.91$; $r^2 > 0.10$) were associated (or trending toward association) with S₁ ($P < 0.011$), DI ($P < 0.036$), and FBG ($P < 0.019$). Association with AIR was not detected. Similar association was detected with individuals in set 2, although many of the SNPs showed a decrease in the magnitude of association. S₁ and FBG were the most consistently associated glucose homeostasis traits, with three of five SNPs in high LD ($D' > 0.77$; $r^2 > 0.08$) showing association or trending toward association ($P < 0.039$ and $P < 0.030$, respectively; Table 3). In the combined analysis (Table 4), the magnitude of association increased within the LD block ($D' > 0.85$, $r^2 > 0.09$; Fig. 1) from that seen in either set independently. S₁ was the most consistently associated trait within the LD block ($P_{\text{meta-analysis}} < 0.0030$). DI was also associated, with four of the five SNPs in high LD showing association ($P_{\text{meta-analysis}} < 0.027$). Association with FBG de-

creased in the combined analysis, and only one SNP remained significant (rs714925, $P_{\text{meta-analysis}} = 0.045$).

DISCUSSION

This study of *SSTR2* gene polymorphisms represents the first detailed population genetic analysis of this gene in relation to glucose homeostasis phenotypes. Whereas the current study design is limited by the SNP selection method, i.e., density versus tagging algorithms, the high LD in the region facilitated sufficient coverage of genetic variation. Strengths of this study include the use of a large Hispanic-American cohort and analysis of quantitative measures of glucose homeostasis. Moreover, since the Hispanic-American subjects were divided into two independent sets with identical recruitment criteria and similar demographic data, results can be compared between the

TABLE 4

Genotypic means for quantitative measures of glucose homeostasis calculated in the combined IRASFS Hispanic-American population

Phenotype	SNP	Alleles†	MAF	Genotypic means \pm SD (<i>n</i>)*			<i>P</i> ‡	<i>P</i> §
				1/1	1/2	2/2		
S _I	rs1037257	C/T	0.38	2.36 \pm 2.04 (350)	2.01 \pm 1.68 (498)	2.22 \pm 2.057 (146)	0.60	0.16
	rs4969076	C/G	0.22	2.21 \pm 1.95 (549)	2.09 \pm 1.72 (360)	2.05 \pm 1.93 (55)	0.43	0.41
	rs1037260	T/G	0.14	2.13 \pm 1.83 (800)	2.26 \pm 2.02 (186)	2.47 \pm 1.63 (7)	0.83	0.75
	rs11077670	G/A	0.12	2.18 \pm 1.92 (716)	2.11 \pm 1.80 (227)	1.92 \pm 1.84 (14)	0.24	0.62
	rs1868486	G/T	0.29	2.23 \pm 1.94 (453)	2.16 \pm 1.86 (423)	1.76 \pm 1.61 (109)	0.000071	0.0025
	rs714925	A/G	0.29	2.23 \pm 1.94 (440)	2.15 \pm 1.85 (434)	1.74 \pm 1.55 (106)	0.0010	0.0030
	rs998571	A/G	0.27	2.25 \pm 1.91 (475)	2.17 \pm 1.89 (397)	1.71 \pm 1.50 (109)	0.00018	0.0024
	rs7220818	A/G	0.39	2.02 \pm 1.69 (348)	2.15 \pm 1.86 (487)	2.48 \pm 2.14 (163)	0.60	0.16
	rs6501603	T/G	0.47	2.31 \pm 1.99 (293)	2.07 \pm 1.82 (479)	2.17 \pm 1.79 (201)	0.29	0.13
	rs4969017	T/C	0.03	2.17 \pm 1.89 (946)	1.98 \pm 1.37 (36)	1.01 \pm 0.00 (1)	0.83	0.94
AIR	rs1037257	C/T	0.38	706 \pm 579 (350)	777 \pm 675 (498)	844 \pm 708 (146)	0.32	0.16
	rs4969076	C/G	0.22	781 \pm 640 (549)	721 \pm 635 (360)	800 \pm 719 (55)	0.48	0.66
	rs1037260	T/G	0.14	754 \pm 659 (800)	814 \pm 643 (186)	496 \pm 147 (7)	0.50	0.78
	rs11077670	G/A	0.12	772 \pm 629 (716)	730 \pm 725 (227)	882 \pm 586 (14)	0.37	0.55
	rs1868486	G/T	0.29	747 \pm 599 (453)	799 \pm 715 (423)	710 \pm 664 (109)	0.43	0.58
	rs714925	A/G	0.29	750 \pm 598 (440)	798 \pm 711 (434)	711 \pm 675 (106)	0.48	0.56
	rs998571	A/G	0.27	751 \pm 590 (475)	796 \pm 730 (397)	731 \pm 667 (109)	0.99	0.99
	rs7220818	A/G	0.39	776 \pm 636 (348)	762 \pm 687 (487)	741 \pm 601 (163)	0.90	0.96
	rs6501603	T/G	0.47	735 \pm 592 (293)	771 \pm 674 (479)	786 \pm 692 (201)	0.46	0.47
	rs4969017	T/C	0.03	756 \pm 641 (946)	871 \pm 839 (36)	195 \pm 0 (1)	0.75	0.25
DI	rs1037257	C/T	0.38	1,332 \pm 1,179 (350)	1,290 \pm 1,221 (498)	1,444 \pm 1,408 (146)	0.56	0.92
	rs4969076	C/G	0.22	1,409 \pm 1,344 (549)	1,186 \pm 1,018 (360)	1,357 \pm 1,380 (55)	0.051	0.036
	rs1037260	T/G	0.14	1,287 \pm 1,201 (800)	1,474 \pm 1,362 (186)	1,275 \pm 910 (7)	0.82	0.90
	rs11077670	G/A	0.12	1,376 \pm 1,277 (716)	1,137 \pm 1,056 (227)	1,575 \pm 1,615 (14)	0.00025	0.015
	rs1868486	G/T	0.29	1,335 \pm 1,225 (453)	1,385 \pm 1,295 (423)	1,030 \pm 1,107 (109)	0.00037	0.0075
	rs714925	A/G	0.29	1,333 \pm 1,209 (440)	1,373 \pm 1,250 (434)	1,009 \pm 1,076 (106)	0.0010	0.0061
	rs998571	A/G	0.27	1,365 \pm 1,233 (475)	1,373 \pm 1,299 (397)	1,028 \pm 1,064 (109)	0.0030	0.027
	rs7220818	A/G	0.39	1,326 \pm 1,242 (348)	1,277 \pm 1,203 (487)	1,450 \pm 1,285 (163)	0.070	0.14
	rs6501603	T/G	0.47	1,391 \pm 1,320 (293)	1,265 \pm 1,169 (479)	1,355 \pm 1,177 (201)	0.30	0.24
	rs4969017	T/C	0.03	1,326 \pm 1,252 (946)	1,295 \pm 1,087 (36)	197 \pm 0 (1)	0.66	0.47
FBG	rs1037257	C/T	0.38	93.03 \pm 9.60 (371)	93.65 \pm 9.72 (529)	93.31 \pm 8.74 (151)	0.21	0.87
	rs4969076	C/G	0.22	93.46 \pm 9.75 (589)	93.13 \pm 9.10 (374)	94.01 \pm 9.65 (58)	0.47	0.54
	rs1037260	T/G	0.14	93.33 \pm 9.51 (848)	93.38 \pm 9.37 (194)	92.95 \pm 10.49 (10)	0.91	0.74
	rs11077670	G/A	0.12	93.21 \pm 9.56 (763)	93.89 \pm 9.63 (236)	96.93 \pm 8.97 (14)	0.056	0.11
	rs1868486	G/T	0.29	92.90 \pm 9.63 (484)	93.52 \pm 9.44 (442)	95.31 \pm 9.52 (116)	0.010	0.083
	rs714925	A/G	0.29	92.81 \pm 9.56 (473)	93.49 \pm 9.41 (452)	95.34 \pm 9.66 (113)	0.010	0.045
	rs998571	A/G	0.27	92.83 \pm 9.48 (509)	93.51 \pm 9.57 (415)	94.90 \pm 9.75 (115)	0.010	0.079
	rs7220818	A/G	0.39	93.87 \pm 11.96 (365)	93.44 \pm 10.97 (513)	91.96 \pm 9.74 (178)	0.10	0.25
	rs6501603	T/G	0.47	93.17 \pm 9.49 (313)	93.71 \pm 9.82 (510)	93.03 \pm 9.02 (208)	0.76	0.72
	rs4969017	T/C	0.03	93.40 \pm 9.49 (1000)	91.64 \pm 9.21 (40)	93.00 \pm 0.00 (1)	0.41	0.81

Boldface data indicate *P* values < 0.05 . *Genotypic means \pm SD (*n*) for homozygotes of the major allele (1/1) as well as heterozygotes (1/2) and homozygotes of the minor allele (2/2). †Major/minor alleles. ‡Test for association among each SNP-trait combination using a series of generalized estimating equations. §Meta-analysis *P* value computed by sequential oligogenic linkage analysis with the modeling of set 1 or set 2 affiliation as a random effect in a variance component-measured genotype model.

two populations, resulting in an ideal replication population, and can be combined to give maximal power for detecting association.

In total, 10 SNPs located at the *SSTR2* locus were genotyped on 1,425 Hispanic Americans. The most consistent region of association fell within the LD block encompassing the *SSTR2* gene, with three of the five SNPs highly correlated ($r^2 > 0.78$; Fig. 1) and driving the association. IRASFS Hispanic Americans were separated into two distinct groups for analysis, and results were compared between groups. Although set 1 individuals exhibited stronger association between polymorphisms in *SSTR2* and S_I as well as DI and FBG, similar evidence of association or trends was detected in set 2, albeit of lesser magnitude. Thus, association was detected in two independent sets of Hispanic Americans.

The magnitude of association increased when the two sets of Hispanic Americans were combined. Tests of between-population heterogeneity were nonsignificant for the most significantly associated SNPs and traits (Table A2 in the online appendix). Within the LD block, associations were observed between *SSTR2* SNPs and S_I ($P_{\text{meta-analysis}} = 0.0024-0.0030$) and DI ($P_{\text{meta-analysis}} = 0.0075-0.027$). Examination of the genotypic means revealed a consistent pattern of decreased S_I ($\beta_{\text{homozygous}} = -0.16$) and DI ($\beta_{\text{homozygous}} = -0.35$ to -5.16) associated with the minor allele (Table 4; online appendix Table A2). In addition, evidence of association was observed with FBG ($P_{\text{meta-analysis}} = 0.045$), with increased values ($\beta_{\text{homozygous}} = 2.30$) associated with the minor allele (Table 4; online appendix Table A2). Taken together, these findings are consistent with genetic variants at the *SSTR2* locus contributing to insulin resistance, which

results in higher circulating blood glucose levels. Evaluation of *SSTR2* SNPs for association with type 2 diabetes resulted in an overall lack of association, with only a single SNP showing nominal association (rs7220818, $P = 0.040$; data not shown). Lack of association should be viewed cautiously, as the result could be attributed to modest sample size for type 2 diabetes ($n = 181$).

In addition, we evaluated *SSTR2* in a collection of 605 African Americans from the IRASFS who were recruited and phenotyped in a similar manner. No evidence of association was observed (data not shown). This absence of association could reflect observable differences in LD patterns in the Hispanic- and African-American populations as reflected in the HapMap reference populations (CEU and YRI, respectively; online appendix Figs. A1 and A2), which results in less efficient tagging of variation in African populations ($r^2 = 0.47$, $MAF > 0.05$, aggressive tagging algorithm). In addition, lack of association could be attributed to reduced power due to smaller sample size or ethnicity-specific genetic differences.

SSTR2 polymorphisms appear to play a role in the modulation of glucose homeostasis through mechanisms consistent with the known biological function of the protein. SRIF inhibits growth hormone and glucagon secretion in a subtype-selective process through *SSTR2* (1). Both growth hormone and glucagon exhibit potent antagonistic effects on insulin action by increasing hepatic gluconeogenesis and glycogenolysis. In addition, growth hormone decreases peripheral glucose utilization (20). Decreased utilization of peripheral glucose would directly affect S_I as measured herein. Evidence of association with DI is likely to be attributed to associations with S_I due to the mathematical relationship ($DI = S_I \times AIR$). The physiological effect of decreased glucose utilization coupled with increased glucose production would result in elevated blood glucose levels, as observed through the association with FBG. Lack of association with AIR could be attributed to the subtype-selective actions of SRIF to inhibit insulin secretion, predominantly through *SSTR5* (1).

Based on these findings, additional research is warranted to identify a true functional variant(s), as it is unlikely the causal variant was genotyped on these individuals; i.e., SNPs were chosen based on position. Although evidence of association was detected between SNPs in the *SSTR2* coding region and glucose homeostasis phenotypes, magnitude of the association was not completely consistent throughout all analyses, suggesting that the association is due to LD with the true functional variant. Additionally, a more thorough evaluation of the proximal 5' genomic region may provide insight into a causal mechanism, possibly through interaction with the proposed promoter(s) (21–23). In conclusion, *SSTR2* polymorphisms are associated with glucose homeostasis and appear to be involved through modulation of S_I .

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