# Genome-Wide Association Study of Serum Fructosamine and Glycated Albumin in Adults Without Diagnosed Diabetes: Results From the Atherosclerosis Risk in Communities Study

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Fructosamine and glycated albumin are potentially useful alternatives to hemoglobin A<sub>1c</sub> (HbA<sub>1c</sub>) as diabetes biomarkers. The genetic determinants of fructosamine and glycated albumin, however, are unknown. We performed genome-wide association studies of fructosamine and glycated albumin among 2,104 black and 7,647 white participants without diabetes in the Atherosclerosis Risk in Communities (ARIC) Study and replicated findings in the Coronary Artery Risk Development in Young Adults (CARDIA) study. Among whites, rs34459162, a novel missense single nucleotide polymorphism (SNP) in RCN3, was associated with fructosamine ( $P = 5.3 \times 10^{-9}$ ) and rs1260236, a known diabetes-related missense mutation in GCKR, was associated with percent glycated albumin  $(P = 5.9 \times 10^{-9})$  and replicated in CARDIA. We also found two novel associations among blacks: an intergenic SNP, rs2438321, associated with fructosamine ( $P = 6.2 \times 10^{-9}$ ), and an intronic variant in PRKCA, rs59443763, associated with percent glycated albumin ( $P = 4.1 \times 10^{-9}$ ), but these

results did not replicate. Few established fasting glucose or  $HbA_{1c}$  SNPs were also associated with fructosamine or glycated albumin. Overall, we found genetic variants associated with the glycemic information captured by fructosamine and glycated albumin as well as with their nonglycemic component. This highlights the importance of examining the genetics of hyperglycemia biomarkers to understand the information they capture, including potential glucose-independent factors.

Diabetes is defined by elevated blood glucose levels (hyperglycemia). Hemoglobin  $A_{1c}$  (Hb $A_{1c}$ ) is formed as glucose binds to hemoglobin molecules within erythrocytes and is the standard clinical measure of chronic hyperglycemia used to diagnose and monitor diabetes (1). However, factors related to the nonglycemic portion of Hb $A_{1c}$  such as erythrocyte turnover and hemoglobin characteristics can affect Hb $A_{1c}$  values (2).

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There is growing interest in fructosamine and glycated albumin, additional biomarkers of hyperglycemia that demonstrate associations with diabetes risk and complications similar to  $HbA_{1c}$  (3–14). Fructosamine measures total serum protein bound to glucose. Glycated albumin is expressed as a percentage of serum albumin, the most abundant serum protein. Both biomarkers reflect glucose exposure over a shorter period of time (2–4 weeks) than  $HbA_{1c}$  (2–3 months) (15). Fructosamine may be used to monitor glycemic control in clinical situations where  $HbA_{1c}$  is problematic, such as in the setting of anemia or hemoglobinopathies (2). While glycated albumin is not frequently used in the U.S., it is widely used in Japan and other countries as a complement to  $HbA_{1c}$  to monitor short-term glycemic control (16).

The genetics of  $HbA_{1c}$  and glucose have been well studied; however, genetic factors that influence fructosamine and glycated albumin are uncharacterized. Of the known genome-wide association study (GWAS) variants associated with fasting glucose and  $HbA_{1c}$  in European ancestry cohorts, few loci are associated with both (17). Many HbA<sub>1c</sub> variants are in genes related to hematological factors rather than glucose metabolism (18-20), while fasting glucose variants are in genes involved in glucose metabolism (although these variants are not all associated with diabetes) (21–23). This lack of overlap suggests that some underlying genetic variants are specific to particular biomarkers of hyperglycemia rather than to type 2 diabetes. Understanding the genetic determinants of fructosamine and glycated albumin should help in the interpretation of these tests and possibly extend our understanding of the pathophysiology of glucose metabolism. In particular, comparing the genetic overlap between different measures of glycemia may provide insight into the contributions of glycemic versus nonglycemic gene variants, i.e., to what extent genetic factors operate via pathways directly relevant to diabetes pathophysiology ("glycemic") or operate via glycemicindependent pathways that do not influence glucose metabolism or diabetes risk ("nonglycemic," such as the hematological variants associated with HbA<sub>1c</sub>). If nonglycemic genetic variants strongly impact fructosamine and glycated albumin, this may need to be taken into account in the interpretation of these biomarkers as measures of hyperglycemia.

We conducted GWAS of fructosamine and glycated albumin in blacks and whites in the Atherosclerosis Risk in Communities (ARIC) Study. We also compared previously identified genetic determinants for  $HbA_{1c}$  and fasting glucose with fructosamine and glycated albumin to identify common genetic factors related to glucose metabolism and those that may be distinct to fructosamine and glycated albumin.

# RESEARCH DESIGN AND METHODS

# **Study Population**

The ARIC Study is an ongoing prospective cohort of 15,792 participants initiated in 1987 (24). Participants were

middle-aged adults recruited from four U.S. communities (Jackson, Mississippi; Forsyth County, North Carolina; Washington County, Maryland; and suburban Minneapolis, Minnesota). All study participants provided written informed consent, and study protocols were approved by the relevant institutional review boards.

In the current study, we included 9,751 participants (7,647 whites and 2,104 blacks) who attended visit 2 (1990–1992), consented for use of DNA, did not have diagnosed diabetes (self-reported diagnosis or use of diabetes medications), had valid data on fructosamine and glycated albumin, and had genotyping data meeting quality control criteria (Supplementary Fig. 1). Individuals with diagnosed diabetes were excluded to avoid potential bias caused by altered glucose levels as a result of diabetes treatment.

### Genotyping

ARIC Study participants were genotyped using the Affymetrix 6.0 array and imputed separately by race using IMPUTE2 (25) with the 1000 Genomes Project phase 1 (March 2012) reference panel. Quality control excluded individuals based on single nucleotide polymorphism (SNP) mismatch, high discordance with previous TaqMan assay genotypes, genetic outlier status, and relatedness. SNPs with IMPUTE info score <0.8 or minor allele frequency (MAF) <0.05 were excluded. Only autosomal variants (on chromosomes 1–22) were considered. Principal components analysis was used to estimate population substructure with EIGENSTRAT (26).

# **Glycemic Markers**

Fructosamine (Roche Diagnostics, Indianapolis, IN) and glycated albumin and serum albumin (GA-L; Asahi Kasei Pharma Corporation, Tokyo, Japan) were measured in 2012–2013 using a Roche Modular P800 system from serum collected at visit 2 and stored at  $-70^{\circ}$ C (3). Percent glycated albumin was calculated per the manufacturer's protocol: [(glycated albumin concentration in g/dL/serum albumin concentration in g/dL)\*100/1.14] + 2.9. We also examined total glycated albumin (g/dL) as well as serum albumin (g/dL) to help distinguish genetic factors specific to serum protein concentration versus hyperglycemia.

Serum glucose was measured on the Roche Hitachi 911 analyzer using the hexokinase method (Roche Diagnostics), and  $HbA_{1c}$  was measured from whole blood stored at  $-70^{\circ}C$  using high-performance liquid chromatography, standardized to the assay used in the Diabetes Control and Complications Trial (DCCT) (27).

## Statistical Analysis

GWAS in blacks and whites were conducted using SNPTEST v2 (28) for all glycemic biomarkers using imputed allele dosage and controlling for age, sex, field center, and the first 10 principal components under an additive genetic model. Fructosamine and glycated albumin (both percent (%) and total [g/dL]) were transformed

on the natural log scale; therefore, the effect sizes are the change in the natural log of the biomarker per each additional risk allele. Exponentiating the effect sizes thus corresponds to the percent higher or lower biomarker levels per additional risk allele. Fasting glucose and HbA<sub>1c</sub> were not transformed. To identify additional independent SNPs associated with the traits, we performed conditional analyses for genome-wide significant findings. Using fructosamine, percent glycated albumin, and total glycated albumin as the dependent variable and the index SNP (SNP with the lowest P value in a region showing a genome-wide significant association) as a covariate, we evaluated the association between other SNPs with a MAF ≥1% within 250 kB of the index SNP or between recombination hotspots surrounding the index SNP. To estimate percentage of variance explained by each SNP, we used the equation  $R_i^2 = b_i^2 \times$  $var(SNP_i)/var(y)$  where  $b_i$  = the effect size of the association between the SNP<sub>i</sub> and the phenotype y, var(SNP<sub>i</sub>) is 2  $\times$  $MAF_{SNPi} \times (1-MAF_{SNPi})$  and var(y) is the variance in the phenotype (29,30). We meta-analyzed across ancestries using a random-effects model by GWAMA (31).

In sensitivity analyses, we performed GWAS excluding case subjects with undiagnosed diabetes (participants with fasting glucose ≥126 mg/dL or nonfasting glucose >200 mg/dL). To further evaluate the genetic variants pertaining to serum protein levels rather than hyperglycemia, we evaluated the top fructosamine and glycated albumin SNPs for association with total glycated albumin and with serum albumin (transformed on the natural log scale). To determine the extent to which glycemic biomarkers shared genetics, we used the program LDSC, which calculated genetic correlations between the biomarkers from ARIC summary statistics by taking advantage of the LD structure (variants in LD with more SNPs are more likely to have larger effect sizes, which extends to the product of correlated traits). We used precomputed LD scores from 1000 Genomes European data (32). Genetic correlations are not bounded to [-1,1], and estimates outside of this range indicate strong genetic correlations.

## Replication

Significant associations between genetic variants and fructosamine and percent glycated albumin in ARIC were evaluated for replication in the Coronary Artery Risk Development in Young Adults (CARDIA) cohort, a prospective cohort study initiated in 1985 to evaluate risk factors for heart disease among unrelated young adults (33).

Serum specimens from 2005 to 2006 were stored at – 70°C and used to analyze glycated albumin and fructosamine in 2014 using a Roche COBAS 6000 chemistry analyzer (Roche Diagnostics). Glycated albumin and fructosamine were measured using the same assays used in ARIC (glycated albumin by Lucica GA-L from Asahi Kasei Pharma Corporation and fructosamine via Roche Diagnostics).

Genotyping was performed using the Affymetrix 6.0 array. Standard quality control metrics were applied, and

imputation to HapMap Phase II, Build 36, Release 22 was done using MACH (34). Genetic, covariate, fructosamine, and glycated albumin data were available on 1,304 whites and 608 blacks. Individuals with diabetes (current use of glucoselowering medications or fasting glucose ≥126 mg/dL) were excluded from analysis. Linear regression analyses stratified by race were done for the association between significant ARIC SNPs and natural log–transformed fructosamine and percent glycated albumin adjusted for age, sex, field center, and the first three principal components.

Statistical analysis was done using SAS v9.4 (SAS Institute, Cary, NC) (data manipulation) and ProbABELv0.2 (35). If the ARIC SNP was not available in the CARDIA data set, we determined whether proxy SNPs in linkage disequilibrium (LD) with the ARIC SNP ( $r^2 > 0.7$  from 1000 Genomes phase 3v5 European population, GRCh37 assembly using Single Nucleotide Polymorphisms Annotator (SNiPA) [36]) were available and, if so, analyzed the associations with the proxy SNP. We considered a Bonferronicorrected one-sided P value threshold of < 0.05 (0.1/2 SNPs per race) for replication significance. We meta-analyzed ARIC and CARDIA results using fixed-effects inverse variance weighted model by METAL (37).

## **Candidate SNP Analysis**

We additionally evaluated previously identified fasting glucose (n = 41) and HbA<sub>1c</sub> (n = 46) candidate SNPs from the National Human Genome Research Institute (NHGRI)-EBI Catalog of published GWAS using the search terms "fasting glucose" and "HbA1c" (http://www.ebi.ac .uk/gwas/ as of 14 December 2017) for association with fructosamine and percent glycated albumin in ARIC. SNPs were included if they were discovered in European ancestry cohorts, were genome-wide significant ( $P < 5 \times 10^{-8}$ ), and were not in LD with each other ( $r^2 < 0.2$ , using SNiPA) (36). For the candidate SNP analyses, we used a study-wide significance threshold: two traits (fructosamine and glycated albumin), two races (black and white), and the number of candidate SNPs for each trait:  $P < 4.6 \times$  $10^{-4}$  (0.05/(2\*2\*27)) for fasting glucose and P < 2.6 imes $10^{-4}$  (0.05/(2\*2\*49)) for HbA<sub>1c</sub>.

We additionally performed analyses controlling for known fasting glucose and  ${\rm HbA_{1c}}$  SNPs with P < 0.05 in ARIC, compiled into scores calculated as the sum of the number of risk alleles, weighted by the effect size in ARIC among whites.

# Comparison of Variance Explained

To compare the influence of glycemic and nonglycemic genetic variants on fructosamine and glycated albumin to that of  $HbA_{1c}$ , we calculated the percent phenotypic variance explained by the SNPs in our study to those from published results of  $HbA_{1c}$ . In addition, we calculated variance explained by known fasting glucose and albumin SNPs (identified by the same criteria used for fasting glucose and  $HbA_{1c}$ ). Percent variance explained was calculated using the equation described above.

## **RESULTS**

Overall, 7,647 whites and 2,104 blacks from ARIC and 1,304 whites and 608 blacks from CARDIA were included in this study (Supplementary Table 1). Mean age in ARIC (56–57 years) was higher than in CARDIA (45–46 years). The cohorts had similar distribution of sex. CARDIA had a greater percentage of black participants and lower mean values for each measure of glycemia as compared with ARIC.

We identified four genome-wide significant loci in ARIC, two associated with fructosamine and two with percent glycated albumin. Three of these variants, rs34459162 intronic to *RCN3*, rs2438321 (intergenic), and rs59443763 intronic to *PRKCA* have not previously been reported to be associated with any glycemic traits in humans (Table 1). None of the analyses showed evidence for inflation (Supplementary Figs. 2–7).

Among whites, rs34459162 (MAF = 0.08), a missense SNP in RCN3 on chromosome 19, was significantly associated with 1.8% lower fructosamine per minor allele (P =  $5.3 \times 10^{-9}$ , variance explained = 0.6%) (Table 1 and Figs. 1 and 2). This SNP was also associated with total glycated albumin ( $P = 3.8 \times 10^{-8}$ ) (Table 2). The association with percent glycated albumin approached genome-wide significance ( $P = 7.3 \times 10^{-8}$ ), but this SNP was not associated with fasting glucose or HbA<sub>1c</sub> (Table 2). A proxy for rs34459162 (rs8105626, in  $r^2 = 1$  rs34459162) was not associated in CARDIA for association with fructosamine (P = 0.09), although the effect sizes were identical and meta-analysis across the cohorts was significant ( $P = 4.9 \times$ 10<sup>-9</sup>) (Table 1). Conditional analysis in ARIC showed that the additional 63 significant SNPs in the region became nonsignificant after conditioning on rs34459162. In blacks, rs34459162 did not meet the info score >0.8 threshold and thus was not analyzed (Table 2).

Among whites, rs1260326 (also known as rs343480), a known missense mutation in *GCKR* on chromosome 2 (MAF = 0.41), was significantly associated with 1.1% lower levels of percent glycated albumin per minor allele ( $P = 5.3 \times 10^{-9}$ , variance explained = 0.3%) (Supplementary Figs. 8 and 9) (Table 1). The association with percent glycated albumin was also significant in CARDIA (P = 0.04), with similar percent difference (0.8% lower per minor allele) and genome-wide significant meta-analysis results ( $2.3 \times 10^{-8}$ ) (Table 1). The conditional analysis did not reveal additional independent signals in this region. This SNP was not associated with any biomarker among blacks (MAF = 0.14) (Table 2 and Supplementary Table 2), but power was limited, and the meta-analysis across ancestries was not significant (Table 1 and Supplementary Fig. 10).

Among blacks, rs2438321 on chromosome 11 (MAF = 0.11) was associated with 3.5% higher levels of fructosamine per minor allele at a genome-wide significant level ( $P = 6.2 \times 10^{-9}$ , variance explained = 1.8%) (Table 1 and Supplementary Figs. 11 and 12) and approached significance with percent glycated albumin ( $P = 6.4 \times 10^{-5}$ ) and

Table 1—	Geno	me-wide	e signifi	cant loci for	tructo	samir	Table 1— Genome-wide significant loci for fructosamine and percent glycated albumin	ARIC*	cated alk	oumin		CARDIA*			ARIC+CARDIA	ARDIA*		ARIC White+Black*	e+Black*	
		Closest			ı	A1		%		% variance A1	A1		%	P		%				P
rs34459162   19	19	BCN3	C/T	Fructosamine	White	White 0.08	-0.02 (0.003) -2% 5.3E-9	-2%	-2% 5.3E-9	0.6%	0.09	-0.02 (0.014) -2% 0.09	-2% 0.09	0.09	-0.02 (0.003) -2% 4.9E-9	-2%	-2% 4.9E-9	- (°)+	1	1
			!	(µmol/L)		;		!					!			!				
rs1260326	12	GCKR	T/C	Percent glycated albumin (%)	White	White 0.41	-0.01 (0.002) -1%	-1%	5.9E-9	0.3%	0.43	-0.01 (0.004) -1%	-1%	0.04	-0.01 (0.002)	<del>-1</del> %	-1% 2.3E-8	-0.007 (0.005) -0.7% 0.14	-0.7%	0.14
rs2438321   11 <i>CNTN5</i>	⇉	CNTN5	G/A	Fructosamine (µmol/L)	Black	Black 0.11	0.03 (0.006)	3%	6.2E-9	1.8%	0.06	0.006 (0.011) 0.6%	0.6%	0.57	0.03 (0.005)	3%	2.9E-8	0.02 (0.02)	2%	0.37
rs59443763		17 PRKCA	СЛ	Percent glycated albumin (%)	Black	Black 0.06	0.05 (0.009)	5%	4.1E-9	2.0%	I	I	1	I	ı	I	ı	ı	1	ı
Chr, chror White+Bla outcome for respective	noson lck is a or eac	ne; diff, d meta-ar h additic perfect L	lifference nalysis a onal copy _D (r <sup>2</sup> =	Chr, chromosome; diff, difference; freq, frequency. White+Black is a meta-analysis across the ancestric outcome for each additional copy of the minor allele respectively, in perfect LD ( $\ell^2 = 1$ with ARIC SNP)	ncy. *A estries allele, '	\RIC: / in ARI calcult	$V = 7,647$ white IC. †A1 is the nated as $e^{\beta} *100$	es, 2,1 ninor a ).   rs3	04 blacks Ilele in wl 4459162	s; CARDIA: nites. ‡Mea and rs243;	: N = 1 an cha 8321 r	,304 whites, 6 nge in In(outco lot available ir	08 bla ome) f car	ıcks; AF or each DIA dat	RIC+CARDIA is additional A1 a set; evaluate	s a me allele. ed prox	ta-analys §Percent y SNPs r	Chr, chromosome; diff, difference; freq, frequency. *ARIC: $N = 7,647$ whites, 2,104 blacks; CARDIA: $N = 1,304$ whites, 608 blacks; ARIC+CARDIA is a meta-analysis across the cohorts; ARIC White+Black is a meta-analysis across the ancestries in ARIC. †A1 is the minor allele in whites. ‡Mean change in In(outcome) for each additional A1 allele. \$Percent higher or lower levels of the outcome for each additional copy of the minor allele, calculated as $e^{\beta}$ *100.   rs34459162 and rs2438321 not available in CARDIA data set; evaluated proxy SNPs rs8105626 and rs35256014, respectively, in perfect LD ( $r^2 = 1$ with ARIC SNP).	ohorts; · levels ors35256	ARIC of the 3014,

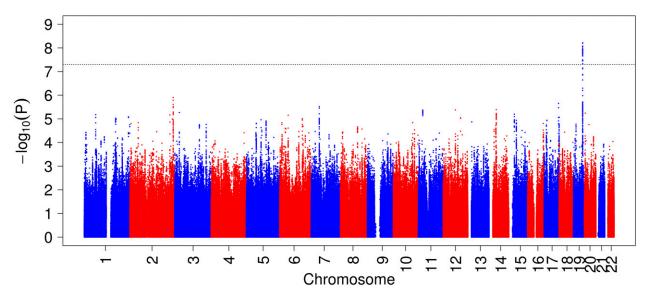


Figure 1 — Manhattan plot for GWAS of fructosamine (log transformed) in whites (N = 7,647).

total glycated albumin ( $P = 2.0 \times 10^{-6}$ ) (Table 2). rs2438321 was not associated with HbA<sub>1c</sub> in blacks and was not associated with any of the markers of hyperglycemia in whites independently or in a meta-analysis across

ancestries (Tables 1 and 2). This SNP was not available in the CARDIA data set; however, a proxy SNP in perfect LD ( $r^2 = 1$ , rs35256014, MAF = 0.06) was present but did not replicate the association with fructosamine in blacks (P = 0.57), and

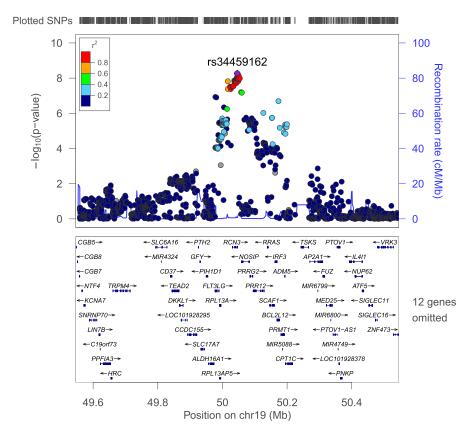


Figure 2—Regional association plot for rs34459162 and fructosamine (log transformed) among whites (included SNPs with MAF ≥5% and imputation quality ≥0.8, insertions and deletions excluded).

	Closest			1000 Genomes	<u>P</u>	Fructosamine (µmol/L)	µmol/L)	Percent glycated albumin (%)	cated %)	Total glycated albumin (g/dL)	albumin	Fasting glucose (mg/dL)	) Jeose	HbA <sub>1c</sub> (%)	9
SNP	gene	A1/A2‡	Race	A1/A2‡ Race A1 freq§ freq	freq	β (SE)	P value	β (SE)	P value	β (SE)	P value	β (SE)	P value	β (SE) P value	Pva
rs34459162	RCN3	С/Т	C/T White	0.08	0.08	-0.02 (0.003) 5.3E-9	5.3E-9	-0.02 (0.004)	7.3E-8	<b>-0.03 (0.005) 3.8E-8</b> 0.26 (0.56) 0.64 -0.02 (0.02) 0.25	3.8E-8	0.26 (0.56)	0.64	-0.02 (0.02)	2.0
			Black	ı	ı	I	ı	) 	ı	ı	ı	ı	ı	I	ı
rs1260326	GCKR	T/C	White Black	0.43 0.10	0.41 0.14	-0.003 (0.002) 0.0005 (0.005)	0.02	<b>-0.01 (0.002)</b> -0.0003 (0.006)	<b>5.9E-9</b> 0.96	-0.01 (0.003) 1.3E-5 -1.13 (0.28) 4.5E-5 -0.01 (0.008) 0.001 (0.009) 0.9 -0.53 (1.16) 0.64 -0.01 (0.04)	1.3E-5 0.9	-1.13 (0.28) -0.53 (1.16)	4.5E-5 0.64	1.3E-5 -1.13 (0.28) 4.5E-5 -0.01 (0.008) 0.09 0.9 -0.53 (1.16) 0.64 -0.01 (0.04) 0.76	0.09 0.76
rs2438321	CNTN5	G/A	White	0.30	0.24	-0.001 (0.002)	0.44	0.0005	0.82	-0.001 (0.003) 0.71	0.71	-0.21 (0.32)	0.52	-0.21 (0.32)   0.52   0.001 (0.01)   0.95	9.0
			Black	0.11	0.11	0.03 (0.006)	6.2E-9	0.03 (0.007)	6.4E-5	0.05 (0.009)	2.0E-6	4.19 (1.24)	8.3E-4	0.05 (0.009) 2.0E-6 4.19 (1.24) 8.3E-4 0.14 (0.04) 6.8E-4	6.8E
rs59443763	PRKCA	C/T	White Black	0.005	0.06	0.04 (0.008) 9.4E-7 <b>0.05 (0.009) 4.1E-9</b>	9 4F-7	- 0.05 (0.009)	- 4.1E-9	_ 0.06 (0.01)	 5.8E-7	— 7.2 (1.65)	9.6E-6		8.3E

meta-analysis results were also nonsignificant (Table 1 and Supplementary Fig. 13).

An intronic variant, rs59443763, in *PRKCA* on chromosome 17 (MAF = 0.06), was significantly associated with 5.4% higher percent glycated albumin per minor allele in blacks ( $P = 4.9 \times 10^{-9}$ , variance explained = 2%) (Table 1 and Supplementary Figs. 14 and 15). It was also associated with fructosamine ( $P = 9.4 \times 10^{-7}$ ) and total glycated albumin ( $P = 5.8 \times 10^{-7}$ ), although these associations did not meet genome-wide significance (Table 2). This SNP was not significant among whites or in trans-ancestry meta-analysis (Tables 1 and 2), but there was limited power to replicate (Supplementary Table 2). No proxy SNPs with  $r^2 > 0.7$  were available in the CARDIA data set, and thus replication was not possible for this association.

# **Sensitivity Analyses**

In analyses that excluded participants with undiagnosed diabetes, genome-wide significant results remained for the white sample (N=7,229) but were no longer present among the reduced sample of black participants (N=1,878) (Supplementary Table 3).

Of the SNPs significantly associated with fructosamine or glycated albumin, only rs2438321 in blacks (P = 0.002) was significantly associated with serum albumin with a Bonferroni corrected P value (0.05/(4 SNPs \* 2 races) = 0.006) (Supplementary Table 4).

Controlling for fasting glucose or  $\mathrm{HbA}_{1c}$  variants did not reveal any additional genome-wide significant variants, but for glycated albumin, controlling for fasting glucose score attenuated the P value for rs1260326 (P = 0.002) among whites.

Fructosamine, percent glycated albumin, and total glycated albumin had strong, statistically significant genetic correlations (0.92 to 1.17) indicating a large proportion of shared genetics (Supplementary Table 5). Correlations between fasting glucose and  $HbA_{1c}$  with the other biomarkers were moderate to substantial but were not significant.

## **Candidate SNP Analysis**

We investigated SNPs previously identified in fasting glucose and  ${\rm HbA_{1c}}$  GWAS for association with fructosamine and percent glycated albumin. Nineteen of the 41 fasting glucose SNPs were nominally (P < 0.05) associated with fasting glucose, and 13 of these associations were in the same direction in blacks and whites (Table 3 and Supplementary Table 6) and 33 had consistent direction with the discovery cohort in whites. Four variants (10%) were study-wide significantly associated with fructosamine and percent glycated albumin in whites, three of which were associated with percent glycated albumin and one of which was associated with fructosamine. No variants were study-wide significantly associated with fructosamine or percent glycated albumin in blacks.

Thirty-one of 46 previously identified  $HbA_{1c}$  SNPs were nominally associated with  $HbA_{1c}$ , 15 of which were associated

Table 3-Significance of associations between fasting glucose known genetic determinants and fructosamine and percent glycated albumin in ARIC Blacks

Chiposolion         All Pollule placed of the procession of the proces	Christostion         And P value         P value p value glycated proteined							Whites				Blacks	
12.132041618         Papical and Markells         G/4         0.33         0.95         0.76         0.14         0.17         0.11         0.11           11.5320604168         Papical and Markells         G/C         0.28         0.001         0.003         3.38E-07         0.07         0.13         0.03           11.5320604710         And Alexandria         G/C         0.28         0.001         0.015         0.06         0.03         0.04         0.03 <t< th=""><th>11.13204161         PPRNZ         GA         0.33         0.95         0.76         0.14         0.16         0.17         0.11           11.13270810         MINAPIB         GAC         0.28         0.001         0.003         33E-07         0.07         0.13         0.03           11.13270810         ADAPA         1.12         0.82         0.001         0.035         0.03         0.04         0.03         0.03         0.03         0.03         0.03         0.03         0.03         0.04         0.04         0.05         0.04         0.05         0.03         0.04         0.04         <t< th=""><th></th><th>Chr.position</th><th>Closest gene</th><th>A1/A2</th><th>fred fred</th><th>P value fructosamine</th><th><b>8</b></th><th>P value fasting glucose</th><th>A1 freq</th><th>P value fructosamine</th><th>P value glycated albumin</th><th>P value fasting glucose</th></t<></th></t<>	11.13204161         PPRNZ         GA         0.33         0.95         0.76         0.14         0.16         0.17         0.11           11.13270810         MINAPIB         GAC         0.28         0.001         0.003         33E-07         0.07         0.13         0.03           11.13270810         ADAPA         1.12         0.82         0.001         0.035         0.03         0.04         0.03         0.03         0.03         0.03         0.03         0.03         0.03         0.04         0.04         0.05         0.04         0.05         0.03         0.04         0.04 <t< th=""><th></th><th>Chr.position</th><th>Closest gene</th><th>A1/A2</th><th>fred fred</th><th>P value fructosamine</th><th><b>8</b></th><th>P value fasting glucose</th><th>A1 freq</th><th>P value fructosamine</th><th>P value glycated albumin</th><th>P value fasting glucose</th></t<>		Chr.position	Closest gene	A1/A2	fred fred	P value fructosamine	<b>8</b>	P value fasting glucose	A1 freq	P value fructosamine	P value glycated albumin	P value fasting glucose
11.97.09710         MTMRHS         GVC         0.28         0.001         0.003         3.8E-OT         0.07         0.13         0.03           0.11.90.20030         MTMRHS         GVC         0.28         0.075         0.75         0.08         0.24         0.07           0.11.50.20030         GVA         0.38         0.60         0.91         0.75         0.09         0.09           1.11.54.20086         GVA         0.32         0.005         0.58         0.09         0.09         0.09           1.11.54.20086         ARAPT         AKG         0.16         0.01         0.09         0.09         0.09         0.09           1.11.54.20086         ARAPT         AKG         0.16         0.01         0.09         0.04         0.09 <td< td=""><td>11.827.08710         MTMPHS         G/C         C.88         0.001         0.003         33E-07         0.07         0.13         0.003           11.827.08710         MTMPHS         G/C         C.88         0.001         0.75         0.76         0.09         0.21         0.05           15.824.32802         G/C         C.20A8         G/A         0.32         0.005         0.81         0.09         0.31         0.09           11.45872037         S/C         C.20A8         G/A         0.32         0.005         0.08         0.09         0.31         0.09           11.45872037         ADAPT         A/C         0.47         0.36         0.00         0.04         0.28         0.09         0.09         0.31         0.09           3.45487039         AMT         T/C         0.37         0.00         0.00         0.04         0.05         0.09<!--</td--><td>083</td><td>12:133041618</td><td>P2RX2</td><td>G/A</td><td>0.33</td><td>0.95</td><td>0.76</td><td>0.14</td><td>0.16</td><td>0.17</td><td>0.11</td><td>0.95</td></td></td<>	11.827.08710         MTMPHS         G/C         C.88         0.001         0.003         33E-07         0.07         0.13         0.003           11.827.08710         MTMPHS         G/C         C.88         0.001         0.75         0.76         0.09         0.21         0.05           15.824.32802         G/C         C.20A8         G/A         0.32         0.005         0.81         0.09         0.31         0.09           11.45872037         S/C         C.20A8         G/A         0.32         0.005         0.08         0.09         0.31         0.09           11.45872037         ADAPT         A/C         0.47         0.36         0.00         0.04         0.28         0.09         0.09         0.31         0.09           3.45487039         AMT         T/C         0.37         0.00         0.00         0.04         0.05         0.09 </td <td>083</td> <td>12:133041618</td> <td>P2RX2</td> <td>G/A</td> <td>0.33</td> <td>0.95</td> <td>0.76</td> <td>0.14</td> <td>0.16</td> <td>0.17</td> <td>0.11</td> <td>0.95</td>	083	12:133041618	P2RX2	G/A	0.33	0.95	0.76	0.14	0.16	0.17	0.11	0.95
11.56.202033         ADPAZA         TyG         0.82         0.75         0.76         0.68         0.24         0.72           11.56.223082         C.2COAMS         Q.M         0.33         0.05         8.2E-65         0.72         0.09         0.93         0.05           8.156.223082         C.2COAMS         Q.M         0.35         0.005         8.2E-65         0.66         0.79         0.98         0.95           11.72-23085         AAPAPI         A/G         0.16         0.005         0.06         0.79         0.99         0.95           3.173065778         ADCYS         A/G         0.16         0.004         0.001         0.06         0.79         0.06         0.79         0.09           3.1730777521         ACY         0.74         0.04         0.004         0.004         0.02         0.04         0.05         0.06         0.78         0.00           3.1730777521         ACYST         A/C         0.31         0.11         0.13         0.13         0.13         0.13         0.13         0.04         0.02         0.06         0.18         0.05         0.00         0.00         0.00         0.00         0.00         0.00         0.00         0.00	(1) (1) (1) (1) (2) (2) (2) (3) (3) (3) (3) (4)         (1) (2) (3) (4)         (1) (2) (3) (4)         (1) (2) (3) (3) (3) (3) (3) (3) (3) (3) (3) (3	6963	11:92708710	MTNR1B	G/C	0.28	0.001	0.003	3.3E-07	0.07	0.13	0.03	0.38
15.66.233962         C2CDAB         G/A         0.38         0.50         0.81         0.55         0.05         0.12         0.08         0.05           81.18.667.33962         C2CDAB         G/A         0.32         0.005         0.28         0.09         0.31         0.01           11.74.367.2086         AAPAPY         A/C         0.47         0.36         0.09         0.04         0.09         0.73         0.05           31.25065778         ADCYS         A/C         0.47         0.39         0.00         0.74         0.06         0.79         0.05           31.25066778         ADCYS         G/A         0.23         0.07         0.001         0.01         0.16         0.02         0.00           31.25066778         ADCYS         G/A         0.23         0.07         0.001         0.01         0.06         0.39         0.05           31.25066778         ADCYS         G/A         0.23         0.04         0.07         0.04         0.03         0.04         0.03         0.05         0.03         0.05         0.03         0.05         0.03         0.05         0.03         0.05         0.03         0.05         0.03         0.04         0.05 <t< td=""><td>14566433962         C2COAB         GAA         0.35         0.65         0.81         0.65         0.15         0.65         0.15         0.05         0.15         0.05         0.05         0.15         0.05</td><td>rs10885122</td><td>10:113042093</td><td>ADRA2A</td><td>1/G</td><td>0.12</td><td>0.82</td><td>0.75</td><td>92'0</td><td>0.68</td><td>0.24</td><td>0.72</td><td>0.21</td></t<>	14566433962         C2COAB         GAA         0.35         0.65         0.81         0.65         0.15         0.65         0.15         0.05         0.15         0.05         0.05         0.15         0.05	rs10885122	10:113042093	ADRA2A	1/G	0.12	0.82	0.75	92'0	0.68	0.24	0.72	0.21
8.118186733         SLC30A8         G.M.         0.05         0.05         0.01         0.01           11.72432886         ARAPT         AG         0.01         0.08         0.47         0.06         0.79         0.05           31.123487388         ARAPT         AG         0.01         0.09         0.04         0.05         0.07           31.123487388         ARAPT         1.7         0.39         0.03         0.01         0.001         0.06         0.08         0.07           31.123468738         ARAT         1.7         0.39         0.30         0.74         0.00         0.09         0.02         0.00         0.07           31.123468738         AGAT         0.13         0.004         0.002         0.04         0.02         0.07         0.002         0.04         0.05         0.00         0.07         0.002         0.04         0.05         0.00         0.07         0.002         0.04         0.05         0.00         0.07         0.002         0.04         0.05         0.06         0.07         0.002         0.04         0.05         0.04         0.05         0.002         0.002         0.002         0.002         0.07         0.02         0.04	8.11818573         SL.C3048         GA         0.005         8.2E-05         1.8E-05         0.03         0.01         0.01         0.01         0.01         0.01         0.01         0.02         0.07         0.03         0.04         0.07         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.05         0.04         0.05         0.04         0.05         0.04         0.05         0.04         0.05         0.04         0.05         0.04         0.05         0.04         0.05         0.04         0.05         0.04         0.05         0.03         0.04         0.05         0.04         0.05         0.04         0.05         0.04         0.05         0.04         0.05         0.04         0.05         0.04         0.05 </td <td>rs11071657</td> <td>15:62433962</td> <td>C2CD4B</td> <td>G/A</td> <td>0.38</td> <td>0.50</td> <td>0.81</td> <td>0.52</td> <td>0.12</td> <td>0.98</td> <td>0.95</td> <td>0.43</td>	rs11071657	15:62433962	C2CD4B	G/A	0.38	0.50	0.81	0.52	0.12	0.98	0.95	0.43
11.72432985         ARAPP1         A/G         0.16         0.01         0.08         0.47         0.06         0.79         0.95           11.42673091         CAR/2         A/C         0.41         0.36         0.68         0.64         0.58         0.07         0.09         0.07           3.132066778         A/C         0.47         0.36         0.074         0.04         0.04         0.04         0.09         0.09         0.09         0.00<	11.72432986         ARAP1         A/G         0.14         0.01         0.08         0.47         0.06         0.79         0.95           11.436473091         ORPZ         A/G         0.47         0.38         0.58         0.66         0.84         0.58         0.09         0.79         0.79         0.79         0.79         0.79         0.79         0.79         0.79         0.00	rs11558471	8:118185733	SLC30A8	G/A	0.32	0.005	8.2E-05	1.8E-05	0.09	0.31	0.18	0.65
11.45873041         CRNZ         AC         0.47         0.36         0.58         0.66         0.84         0.58         0.72           3.132065778         ADCYS         GA         0.23         0.07         0.001         0.01         0.06         0.002         0.003           3.49458303         AMT         17C         0.30         0.034         0.034         0.35         0.07         0.003         0.00         0.003         0.004         0.02         0.04         0.35         0.07         0.03         0.00         0.00         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.34         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03	11:45873091         CRY2         A/C         047         0.36         0.58         0.66         0.84         0.58         0.72           3:422068778         ADCYS         G/A         0.23         0.07         0.001         0.01         0.002         0.002         0.003         0.002         0.003         0.002         0.003         0.002         0.003         0.004         0.002         0.04         0.002         0.04         0.002         0.04         0.002         0.04         0.002         0.04         0.002         0.04         0.002         0.04         0.03         0.04         0.002         0.04         0.04         0.02         0.04         0.02         0.04         0.02         0.04         0.02         0.04         0.02         0.04         0.02         0.04         0.02         0.04         0.04         0.02         0.04         0.02         0.04         0.04         0.02         0.04	rs11603334	11:72432985	ARAP1	A/G	0.16	0.01	0.08	0.47	90.0	0.79	0.95	92'0
3:123065778         ADCY5         G/A         0.23         0.07         0.001         0.04         0.04         0.05         0.002         0.003           3:49453330         AMT         T/C         0.39         0.30         0.74         0.04         0.23         0.06         0.37           5:37577521         S.C2A2         AT         0.13         0.04         0.03         0.04         0.35         0.06         0.37           7         9:8182726         PCSK1         AT         0.13         0.13         0.13         0.13         0.13         0.13         0.14         0.08         0.36         0.18         0.52           7         9:8182703         VPRAZ         AZ         0.13         0.41         0.78         0.74         0.08         0.18         0.18         0.11         0.25         0.11         0.28         0.74         0.08         0.11         0.11         0.11         0.11         0.11         0.11         0.11         0.11         0.11         0.11         0.14         0.28         0.74         0.11         0.11         0.11         0.11         0.11         0.11         0.11         0.11         0.11         0.11         0.11         0.11	3:123065778         ADCY5         G/A         0.23         0.07         0.001         0.002         0.002         0.003           3:349455330         AMT         T/C         0.30         0.30         0.74         0.04         0.02         0.04         0.02         0.04         0.02         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.02         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.03         0.04         0.04         0.03         0.04         0.04         0.04         0.04         0.04         0.04         0.04         0.04         0.04         0.04         0.04         0.04         0.04         0.04         0.04         0.04         0.04         0.04 <td>rs11605924</td> <td>11:45873091</td> <td>CRY2</td> <td>AC</td> <td>0.47</td> <td>0.36</td> <td>0.58</td> <td>99.0</td> <td>0.84</td> <td>0.58</td> <td>0.72</td> <td>0.44</td>	rs11605924	11:45873091	CRY2	AC	0.47	0.36	0.58	99.0	0.84	0.58	0.72	0.44
3:49458330         AMT         T/C         0:30         0:30         0.04         0.04         0.23         0.06         0:37           3:170717521         \$LCZAZ         AT         0:13         0.004         0.02         0.34         0.35         0.47         0.30           5:95642726         AF         0:13         0.014         0.02         0.24         0.36         0.18         0.52           5:95642726         PCSK1         AC         0:31         0.11         0.13         0.14         0.02         0.59         0.18         0.11         0.50           1:48333360         PARST         AC         0:13         0.60         0.78         0.11         0.24         0.04         0.04         0.04         0.04         0.04         0.04         0.05         0.11         0.02         0.04         0.04         0.04         0.04         0.04         0.04         0.04         0.04         0.04         0.04         0.04         0.04         0.04         0.05         0.04         0.05         0.04         0.05         0.04         0.05         0.04         0.05         0.04         0.05         0.05         0.05         0.05         0.05         0.05         0.05 </td <td>3:49455330         AMT         T/C         0:30         0:30         0:04         0:04         0:05         0:06         0:37           3:170717521         SLC2A2         A/T         0:13         0:004         0:002         0:34         0:35         0.47         0:30           5:25752872         A/T         0:13         0:11         0:13         0:11         0:13         0:14         0:13         0:14         0:02         0:34         0:35         0:47         0:03         0:04         0:24         0:35         0:14         0:03         0:04         0:14         0:05         0:18         0:11         0:05         0:18         0:14         0:04         0:24         0:05         0:14         0:05         0:04         0:05         0:14         0:05         0:04         0:05         0:11         0:05         0:14         0:05         0:04         0:05         0:14         0:05         0:04         0:04         0:05         0:04         0:05         0:04         0:05         0:04         0:05         0:04         0:05         0:04         0:05         0:04         0:05         0:04         0:05         0:04         0:05         0:04         0:05         0:04         0:05<td>2908</td><td>3:123065778</td><td>ADCY5</td><td>G/A</td><td>0.23</td><td>0.07</td><td>0.001</td><td>0.01</td><td>0.16</td><td>0.002</td><td>0.003</td><td>0.03</td></td>	3:49455330         AMT         T/C         0:30         0:30         0:04         0:04         0:05         0:06         0:37           3:170717521         SLC2A2         A/T         0:13         0:004         0:002         0:34         0:35         0.47         0:30           5:25752872         A/T         0:13         0:11         0:13         0:11         0:13         0:14         0:13         0:14         0:02         0:34         0:35         0:47         0:03         0:04         0:24         0:35         0:14         0:03         0:04         0:14         0:05         0:18         0:11         0:05         0:18         0:14         0:04         0:24         0:05         0:14         0:05         0:04         0:05         0:14         0:05         0:04         0:05         0:11         0:05         0:14         0:05         0:04         0:05         0:14         0:05         0:04         0:04         0:05         0:04         0:05         0:04         0:05         0:04         0:05         0:04         0:05         0:04         0:05         0:04         0:05         0:04         0:05         0:04         0:05         0:04         0:05         0:04         0:05 <td>2908</td> <td>3:123065778</td> <td>ADCY5</td> <td>G/A</td> <td>0.23</td> <td>0.07</td> <td>0.001</td> <td>0.01</td> <td>0.16</td> <td>0.002</td> <td>0.003</td> <td>0.03</td>	2908	3:123065778	ADCY5	G/A	0.23	0.07	0.001	0.01	0.16	0.002	0.003	0.03
3:3170717521         SLC2A2         AT         0.13         0.004         0.002         0.34         0.35         0.47         0.30           5:95642726         PCSK1         AC         0.31         0.11         0.13         0.61         0.69         0.78         0.78         0.78           2:27162874         PCSK1         AC         0.31         0.11         0.78         0.78         0.18         0.11         0.52           1:148333303         PARALA         CA         0.01         0.65         0.24         0.05         0.73         0.11           9:1148033280         PARKAP         CA         0.01         0.65         0.73         0.68         0.73         0.68           11:61571478         FADS1         CA         0.01         0.02         0.74         0.03         0.73         0.68         0.73         0.68           11:61571478         FADS1         CA         0.13         0.04         0.78         0.74         0.08         0.73         0.68           5:715064309         MAED1         TC         0.26         0.13         0.02         0.04         0.69         0.78         0.78         0.78           7:15064309         TA	3:170717521         SLC2A2         AT         0:13         0.004         0.002         0:34         0:35         0.47         0:30           5:95542726         PCSK1         AV         0:31         0:11         0:13         0:51         0:05         0:05         0:06         0:18         0:05           1:227152874         PPYSL5         TC         0:25         0:47         0:73         0:04         0:05         0:04         0:05         0:11         0:05         0:11         0:05         0:11         0:05         0:11         0:05         0:11         0:05         0:11         0:05         0:11         0:05         0:11         0:05         0:11         0:05         0:11         0:05         0:11         0:05         0:11         0:05         0:12         0:04         0:05         0:04         0:05         0:04         0:05         0:04         0:05         0:04         0:01         0:05         0:04         0:05         0:04         0:05         0:04         0:05         0:04         0:05         0:04         0:05         0:04         0:05         0:04         0:05         0:04         0:05         0:04         0:05         0:04         0:05         0:04         0:05 </td <td>5915</td> <td>3:49455330</td> <td>AMT</td> <td>1/C</td> <td>0.30</td> <td>0:30</td> <td>0.74</td> <td>0.04</td> <td>0.23</td> <td>90.0</td> <td>0.37</td> <td>0.31</td>	5915	3:49455330	AMT	1/C	0.30	0:30	0.74	0.04	0.23	90.0	0.37	0.31
5.95642726         PCSK1         A/C         0.31         0.11         0.13         0.51         0.69         0.59         0.08         0.18         0.52           2.27152874         DPYSL5         T/C         0.25         0.47         0.78         0.69         0.36         0.18         0.11           7 9:96182703         YRNA         C/A         0.01         0.65         0.24         0.55         0.74         0.78         0.79         0.78         0.79         0.78         0.71         0.60         0.78         0.74         0.60         0.78         0.73         0.78         0.73         0.78         0.73         0.78         0.78         0.73         0.78         0.73         0.78         0.78         0.73         0.78         0.78         0.73         0.78         0.78         0.78         0.73         0.78         0.78         0.73         0.78 <td>5.95642726         PCSK1         AVC         0.31         0.11         0.13         0.651         0.69         0.14         0.05           7.996182703         YRNA         CAA         0.01         0.65         0.24         0.55         0.74         0.78         0.68         0.18         0.11           7 9:96182703         YRNA         CAA         0.01         0.65         0.24         0.55         0.14         0.69         0.18         0.11           1 1148333380         ORAST         AVG         0.13         0.41         0.36         0.07         0.04         0.46         0.42           9:111690389         YRRAAP         GYT         0.33         0.16         0.78         0.01         0.66         0.22         0.78         0.01         0.66         0.78         &lt;</td> <td>rs11920090</td> <td>3:170717521</td> <td>SLC2A2</td> <td>Ą</td> <td>0.13</td> <td>0.004</td> <td>0.002</td> <td>0.34</td> <td>0.35</td> <td>0.47</td> <td>0.30</td> <td>0.28</td>	5.95642726         PCSK1         AVC         0.31         0.11         0.13         0.651         0.69         0.14         0.05           7.996182703         YRNA         CAA         0.01         0.65         0.24         0.55         0.74         0.78         0.68         0.18         0.11           7 9:96182703         YRNA         CAA         0.01         0.65         0.24         0.55         0.14         0.69         0.18         0.11           1 1148333380         ORAST         AVG         0.13         0.41         0.36         0.07         0.04         0.46         0.42           9:111690389         YRRAAP         GYT         0.33         0.16         0.78         0.01         0.66         0.22         0.78         0.01         0.66         0.78         <	rs11920090	3:170717521	SLC2A2	Ą	0.13	0.004	0.002	0.34	0.35	0.47	0.30	0.28
DPYSIL5         T/C         0.25         0.47         0.78         0.69         0.36         0.18         0.11           YARNA         C/A         0.01         0.65         0.24         0.55          0.11         0.25         0.73         0.42           ORAST         A/G         0.13         0.41         0.36         0.74         0.04         0.46         0.42         0.42         0.74         0.04         0.46         0.42         0.44         0.45         0.45         0.44         0.45         0.45         0.44         0.45         0.45         0.44         0.45         0.45         0.44         0.45         0.45         0.44         0.45         0.45         0.44         0.45         0.45         0.45         0.44         0.45         0.44         0.45         0.45         0.44         0.45         0.44         0.44         0.44	2:27152874         DPYSL5         T/C         0.25         0.47         0.78         0.69         0.36         0.18         0.11           37         9:96182703         YRMA         C/A         0.01         0.65         0.24         0.55         0.74         0.05         0.24         0.55           3         11:48533360         OPAST         A/G         0.13         0.41         0.36         0.74         0.04         0.46         0.42           4         11:61571478         FABZY         C/T         0.33         0.16         0.28         0.07         0.05         0.75         0.75         0.68           4         6:7131680359         IMBEMYS         G/T         0.28         0.13         0.00         0.11         0.05         0.75         0.05 <td>rs13179048</td> <td>5:95542726</td> <td>PCSK1</td> <td>A/C</td> <td>0.31</td> <td>0.11</td> <td>0.13</td> <td>0.51</td> <td>0.08</td> <td>0.18</td> <td>0.52</td> <td>0.78</td>	rs13179048	5:95542726	PCSK1	A/C	0.31	0.11	0.13	0.51	0.08	0.18	0.52	0.78
97         9.96182703         YRNA         C/A         0.01         0.65         0.24         0.55           11:48333360         OPAST         A/G         0.13         0.41         0.36         0.74         0.04         0.46         0.42           11:48333360         OPAST         A/G         0.13         0.60         0.78         0.11         0.25         0.73         0.68           11:61871478         FADST         C/T         0.33         0.16         0.28         0.001         0.16         0.15         0.15           11:61871478         FADST         C/T         0.33         0.16         0.28         0.001         0.16         0.16         0.15         0.15           11:61871478         FADST         C/T         0.33         0.16         0.32         0.001         0.16         0.16         0.16         0.16         0.16         0.16         0.16         0.16         0.16         0.16         0.16         0.16         0.16         0.16         0.16         0.16         0.16         0.16         0.17         0.16         0.16         0.16         0.16         0.16         0.16         0.16         0.16         0.16         0.16         0.16	97         9.96182703         YRNA         C/A         0.01         0.65         0.24         0.56           11:48333360         OPASI         A/G         0.13         0.41         0.36         0.74         0.04         0.46         0.42           11:48333360         OPASI         A/G         0.13         0.60         0.78         0.11         0.25         0.73         0.68           11:61871478         FADSI         C/T         0.33         0.16         0.28         0.54         0.06         0.37         0.15           4         6:7213200         FREBI         T/C         0.26         0.13         0.28         0.09         0.16         0.16         0.16         0.15         0.15         0.15         0.15         0.16         0.02         0.04         0.16         0.16         0.16         0.16         0.16         0.15         0.15         0.16         0.02         0.04         0.16 <td>614</td> <td>2:27152874</td> <td>DPYSL5</td> <td>1/0</td> <td>0.25</td> <td>0.47</td> <td>0.78</td> <td>69.0</td> <td>0.36</td> <td>0.18</td> <td>0.11</td> <td>0.21</td>	614	2:27152874	DPYSL5	1/0	0.25	0.47	0.78	69.0	0.36	0.18	0.11	0.21
11:48333360         OR4ST         A/G         0:14         0.36         0.74         0.04         0.46         0.42           3 9:111680359         KRBKAP         G/T         0.03         0.60         0.78         0.11         0.25         0.73         0.66           4 6:7213200         RREB1         T/C         0.26         0.13         0.028         0.04         0.06         0.78         0.01         0.05         0.	11:48333360         OR4S1         A/G         0:14         0.36         0.74         0.04         0.46         0.42           3 9:111680359         IKBKAP         G/T         0.03         0.60         0.78         0.11         0.25         0.73         0.66           4 6:7213200         RREB1         T/C         0.26         0.13         0.028         0.041         0.05         0.07         0.15           7 7:15064300         TMEM195, G/T         0.46         0.17         0.36         0.00         0.00         0.00         0.00         0.00         0.00         0.16         0.17         0.16         0.17         0.17         0.18         0.04         0.17         0.18         0.18         0.14         0.18         0.18         0.18         0.14         0.18         0.18         0.14         0.18         0.14         0.18         0.14         0.18         0.14         0.18	29266	9:96182703	YRNA	C/A	0.01	0.65	0.24	0.55				
3         9:111680359         KKBKAP         GT         0.03         0.60         0.78         0.11         0.25         0.73         0.68           11:61571478         FADS1         CT         0.33         0.16         0.28         0.04         0.69         0.37         0.16           4         6:7213200         FABE1         T/C         0.26         0.13         0.32         0.001         0.16         0.16         0.76           7:15064309         TMEM135         GT         0.46         0.17         0.36         0.04         0.16         0.16         0.76           13:28491188         PDX1         A/G         0.22         0.02         0.005         0.03         0.17         0.38         0.76           13:28491188         PDX1         A/G         0.22         0.02         0.005         0.03         0.14         0.58         0.79         0.79           13:28491188         PDX1         A/G         0.12         0.00         0.00         0.02         0.03         0.74         0.58         0.74           13:2849128         GLS2         GA         0.12         0.01         0.04         0.02         0.30         0.64         0.59 <t< td=""><td>3         9:111680359         KKBKAP         GT         0.03         0.60         0.78         0.11         0.25         0.73         0.68           11:61571478         FADS1         CT         0.33         0.16         0.28         0.54         0.08         0.37         0.15           11:61571478         FADS1         CT         0.33         0.16         0.28         0.54         0.09         0.37         0.15           7:15064309         TMEM195         GT         0.46         0.17         0.36         0.00         0.02         0.04         0.16         0.16         0.76           13:28491188         PDX1         A/G         0.22         0.02         0.005         0.03         0.17         0.38         0.73         0.76         0.73         0.76         0.73         0.76         0.73         0.76         0.73         0.76         0.73         0.76         0.73         0.73         0.76         0.73         0.76         0.73         0.76         0.73         0.76         0.73         0.76         0.73         0.74         0.78         0.74         0.78         0.74         0.78         0.74         0.78         0.74         0.78         0.74         0.7</td><td>121</td><td>11:48333360</td><td>OR4S1</td><td>A/G</td><td>0.13</td><td>0.41</td><td>0.36</td><td>0.74</td><td>0.04</td><td>0.46</td><td>0.42</td><td>0.94</td></t<>	3         9:111680359         KKBKAP         GT         0.03         0.60         0.78         0.11         0.25         0.73         0.68           11:61571478         FADS1         CT         0.33         0.16         0.28         0.54         0.08         0.37         0.15           11:61571478         FADS1         CT         0.33         0.16         0.28         0.54         0.09         0.37         0.15           7:15064309         TMEM195         GT         0.46         0.17         0.36         0.00         0.02         0.04         0.16         0.16         0.76           13:28491188         PDX1         A/G         0.22         0.02         0.005         0.03         0.17         0.38         0.73         0.76         0.73         0.76         0.73         0.76         0.73         0.76         0.73         0.76         0.73         0.76         0.73         0.73         0.76         0.73         0.76         0.73         0.76         0.73         0.76         0.73         0.76         0.73         0.74         0.78         0.74         0.78         0.74         0.78         0.74         0.78         0.74         0.78         0.74         0.7	121	11:48333360	OR4S1	A/G	0.13	0.41	0.36	0.74	0.04	0.46	0.42	0.94
11:61571478         FADS1         C/T         0.33         0.16         0.28         0.54         0.09         0.37         0.15           4         6:7213200         RREB1         T/C         0.26         0.13         0.32         0.001         0.16         0.16         0.16         0.16           7:15064309         RMEB1         T/C         0.26         0.13         0.36         0.005         0.007         0.04         0.16         0.16         0.17         0.17         0.17         0.17         0.17         0.17         0.17         0.17         0.17         0.17         0.17         0.17         0.17         0.17         0.18         0.17         0.18         0.14         0.18         0.14         0.18         0.14         0.18         0.14         0.18         0.17         0.18         0.17         0.18         0.17         0.18         0.14         0.18         0.14         0.18         0.14         0.18         0.14         0.18         0.14         0.18         0.14         0.18         0.14         0.18         0.14         0.18         0.12         0.14         0.18         0.14         0.18         0.14         0.18         0.12         0.14         0.18	4         6:7213200         FABS1         C/T         0.33         0.16         0.28         0.54         0.08         0.37         0.15           4         6:7213200         FREB1         T/C         0.26         0.13         0.32         0.001         0.16         0.16         0.76           7:15064309         TMEN195, GT         0.46         0.17         0.36         0.03         0.04         0.16         0.16         0.76           13:28491188         PDX1         A/G         0.22         0.02         0.03         0.17         0.38         0.73           13:28491188         PDX1         A/G         0.22         0.02         0.005         0.04         0.02         0.04         0.05         0.73         0.79           13:28491188         PDX1         A/G         0.22         0.02         0.04         0.02         0.04         0.05         0.07         0.79         0.79         0.77         0.89         0.77         0.89         0.74         0.89         0.74         0.89         0.74         0.89         0.74         0.78         0.74         0.78         0.74         0.74         0.78         0.74         0.78         0.74         0.78 <td< td=""><td>3693</td><td>9:111680359</td><td>IKBKAP</td><td>G/T</td><td>0.03</td><td>09.0</td><td>0.78</td><td>0.11</td><td>0.25</td><td>0.73</td><td>0.68</td><td>0.91</td></td<>	3693	9:111680359	IKBKAP	G/T	0.03	09.0	0.78	0.11	0.25	0.73	0.68	0.91
4         6:7213200         PREB1         T/C         0.26         0.13         0.02         0.04         0.16         0.16         0.76           7:15064309         TMEM195, DGKB         G/T         0.44         0.17         0.36         0.04         0.58         0.73           13:28491198         PDX1         A/G         0.22         0.02         0.005         0.03         0.17         0.38         0.07           19:46196634         GIPP         G/C         0.50         1.00         0.40         0.02         0.30         0.64         0.59           19:46196634         GIPP         G/C         0.50         1.00         0.40         0.02         0.30         0.64         0.59           12:15686538         GLSZ         G/A         0.18         0.93         0.94         0.31         0.62         0.29         0.69         0.37         0.64         0.93           12:10486528         G/A         0.16         0.42         0.82         0.42         0.82         0.45         0.75         0.75         0.74         0.74         0.74         0.74         0.74         0.74         0.74         0.74         0.74         0.74         0.74         0.74	4         6:7213200         FMEB1         T/C         0.26         0.13         0.32         0.001         0.16         0.16         0.76           7:15064309         TMEM195, DGKB         GT         0.46         0.17         0.36         0.02         0.03         0.04         0.58         0.73           13:28491198         PDX1         A/G         0.22         0.02         0.005         0.005         0.03         0.17         0.38         0.09           13:28491198         PDX1         A/G         0.20         0.002         0.005         0.03         0.17         0.38         0.09           13:28401198         PDX1         A/G         0.20         0.00         0.40         0.02         0.03         0.09	20	11:61571478	FADS1	C	0.33	0.16	0.28	0.54	0.08	0.37	0.15	0.93
7:15064309         TIMEM195, DGKB         GT         0.46         0.17         0.36         0.02         0.03         0.04         0.58         0.77         0.60           13:28491198         PDX1         A/G         0.22         0.02         0.005         0.03         0.17         0.38         0.60           19:46196634         GIPR         G/C         0.50         1.00         0.40         0.02         0.30         0.64         0.94           19:46196634         GIPR         G/C         0.50         1.00         0.40         0.02         0.30         0.64         0.94           11:56865338         GLSZ         G/A         0.18         0.93         0.94         0.31         0.06         0.05         0.03         0.23           1:214159266         PROX1         T/C         0.12         0.04         0.82         0.40         0.17         0.26         0.35         0.14         0.16         0.74         0.26         0.43         0.10         0.14         0.16         0.05         0.25         0.43         0.10         0.10         0.10         0.10         0.10         0.10         0.10         0.10         0.11         0.16         0.12         0.12	7:15064309         TMEM195, DGKB         GT         0.46         0.17         0.36         0.02         0.04         0.58         0.73           13:28491198         PDX1         A/G         0.22         0.02         0.005         0.03         0.17         0.38         0.60           19:46196634         GIPR         G/C         0.50         1.00         0.40         0.02         0.30         0.64         0.94         0.99         0.64         0.94         0.99         0.64         0.99         0.94         0.31         0.06         0.09         0.99         0	2454	6:7213200	RREB1	1/0	0.26	0.13	0.32	0.001	0.16	0.16	0.76	0.75
13:28491198         PDX1         A/G         0.22         0.02         0.005         0.03         0.03         0.17         0.38         0.60           19:46196634         GIPR         G/C         0.50         1.00         0.40         0.02         0.30         0.64         0.94           12:56865338         GLSZ         G/A         0.18         0.93         0.94         0.31         0.06         0.05         0.23           12:56865338         GLSZ         G/A         0.18         0.93         0.94         0.31         0.06         0.05         0.23           12:14592766         PROXT         T/C         0.42         0.01         0.07         0.26         0.74         0.74         0.74           12:10287569         IGFT         G/A         0.16         0.76         0.62         0.43         0.74         0.74         0.74           12:10287569         IGFT         G/A         0.26         0.11         0.07         0.25         0.43         0.75         0.06         0.44         0.60           2:27995781         IMPLZ         A/G         0.26         0.13         0.16         0.75         0.06         0.44         0.60	13:28491198         PDX1         A/G         0.22         0.002         0.005         0.03         0.17         0.38         0.60           19:46196634         GIPR         G/C         0.50         1.00         0.40         0.02         0.30         0.64         0.94           12:56866338         GLSZ         G/A         0.18         0.93         0.94         0.31         0.06         0.05         0.23           8:40484239         ZMAT4         T/C         0.12         0.01         0.01         0.78         0.25         0.25         0.23           1:21102875569         PPOXT         T/C         0.45         0.42         0.82         0.40         0.77         0.25         0.35           12:10287569         IGFT         G/F         0.14         0.07         0.62         0.43         0.10         0.10           2:27995781         WAPLS         T/G         0.26         0.11         0.07         0.25         0.43         0.07         0.03           11:114756041         TCF1L2         T/A         0.21         0.03         0.13         0.04         0.01         0.04         0.09         0.04         0.00           10:114756041         TCF	349	7:15064309	TMEM195, DGKB	G/T	0.46	0.17	0.36	0.02	0.44	0.58	0.73	0.004
19.46196634         GIPR         G/C         6.50         1.00         0.40         0.02         0.30         0.64         0.94           12:56865338         GLSZ         G/A         0.18         0.93         0.94         0.31         0.06         0.05         0.23           8:40484239         ZMAT4         T/C         0.12         0.01         0.01         0.01         0.78         0.37         0.25         0.23           1:214159256         PROX7         T/C         0.45         0.42         0.82         0.40         0.17         0.36         0.74           12:10287569         IGF1         G/A         0.16         0.76         0.54         0.62         0.55         0.43         0.10           2:27995781         MRPL33         C/A         0.26         0.11         0.07         0.25         0.43         0.10         0.03           14:100839261         WARS         T/G         0.26         0.45         0.51         0.51         0.65         0.43         0.00         0.44         0.00           9:139256766         DNLZ         T/G         0.29         0.03         0.14         0.09         0.44         0.09         0.40	19:46196634         GIPR         G/C         6:50         1.00         0.40 <b>0.02</b> 0.30         0.64         0.94           12:56865338         GLSZ         G/A         0:18         0.93         0.94         0.31         0.06         0.05         0.23           8:40484239         ZMAT4         T/C         0:12         0.01         0.01         0.78         0.25         0.25         0.35         0.35           1:214159256         PROX1         T/C         0:45         0.04         0.08         0.40         0.17         0.36         0.74         0.74           12:10287569         IGF1         G/A         0:16         0.76         0.54         0.62         0.55         0.43         0.10           2:27995781         MRPL33         C/A         0:16         0.76         0.51         0.62         0.55         0.43         0.10           14:100839261         WARS         T/G         0:22         0.45         0.51         0.57         0.06         0.44         0.60           9:139256766         DNLZ         A/G         0:29         0.03         0.13         0.05         0.14         0.09         0.44         0.60	941	13:28491198	PDX1	A/G	0.22	0.02	0.005	0.03	0.17	0.38	09.0	0.77
12:56865338         GLSZ         G/A         0.18         0.93         0.94         0.31         0.06         0.05         0.23           8:40484239         ZMA74         T/C         0.12         0.01         0.01         0.78         0.37         0.25         0.35           1:214159256         PROX1         T/C         0.45         0.42         0.82         0.40         0.17         0.36         0.74           12:102875569         IGF1         G/A         0.16         0.76         0.54         0.62         0.73         0.73         0.10           2:27995781         MAPPL33         C/A         0.26         0.11         0.07         0.25         0.43         0.10         0.03           14:100839261         WAPS         T/G         0.26         0.11         0.07         0.57         0.06         0.44         0.60           9:139256766         DNLZ         A/G         0.29         0.03         0.15         0.16         0.16         0.16         0.09         0.19         0.09           9:139256766         DNLZ         A/G         0.2         0.04         0.16         0.14         0.09         0.41         0.09           7:44235668	12:56865338         GLSZ         G/A         0.18         0.93         0.94         0.31         0.06         0.05         0.23           8:40484239         ZMAT4         T/C         0.12         0.01         0.01         0.78         0.37         0.25         0.35           1:214159256         PROXT         T/C         0.12         0.04         0.82         0.40         0.17         0.36         0.74           12:102875569         IGF1         G/A         0.16         0.76         0.54         0.62         0.43         0.10         0.74           14:10287569         IGF1         G/A         0.26         0.11         0.07         0.25         0.43         0.07         0.03           14:100839261         WARS         T/G         0.22         0.45         0.51         0.57         0.06         0.44         0.00           9:139256766         DNLZ         A/G         0.29         0.003         0.13         0.16         0.14         0.09         0.40         0.09           10:114756041         TCF7L2         T/A         0.31         3.9E-04         2.5E-05         0.74         0.09         0.40         0.10           7:44235668	593	19:46196634	GIPR	G/C	0.50	1.00	0.40	0.02	0.30	0.64	0.94	0.97
8:40484239         ZMAT4         T/C         0.12         0.01         0.01         0.78         0.25         0.36           1:214159256         PROX1         T/C         0.45         0.42         0.82         0.40         0.17         0.36         0.74           12:102875569         IGF1         G/A         0.16         0.76         0.54         0.60         0.74         0.70           2:27995781         MRPL33         C/A         0.26         0.11         0.07         0.25         0.43         0.07         0.03           14:100839261         WARS         T/G         0.29         0.045         0.51         0.57         0.06         0.44         0.60           9:139256766         DNLZ         A/G         0.29         0.003         0.13         0.16         0.16         0.44         0.60           10:114756041         TCF7L2         T/A         0.31         3.9E-04         2.5E-05         2.7E-05         0.44         0.09         0.40           7:44235668         GCK         A/G         0.17         2.0E-04         0.003         0.11         0.05         0.11         0.09         0.11         0.09         0.10         0.09         0.10	8:40484239         ZMMT4         T/C         0.12         0.01         0.01         0.78         0.25         0.25         0.36           1:214159256         PROX1         T/C         0.45         0.42         0.82         0.40         0.17         0.36         0.74           12:102875569         IGF1         G/A         0.16         0.76         0.54         0.62         0.43         0.10           2:27995781         MRPL33         C/A         0.26         0.11         0.07         0.25         0.43         0.01           14:100839261         WARS         T/G         0.22         0.45         0.51         0.67         0.06           9:139256766         DNLZ         A/G         0.29         0.003         0.13         0.16         0.18         0.51         0.09           10:114756041         TCF7L2         T/A         0.31         3.9E-04         2.5E-05         2.7E-05         0.44         0.09         0.40           7:44235668         GCK         A/G         0.17         2.0E-04         0.003         5.0E-04         0.01         0.11         0.09         0.11           8:9183596         PPP1R3B         A/G         0.99         0.33	879	12:56865338	GLS2	G/A	0.18	0.93	0.94	0.31	90.0	0.05	0.23	0.04
1:214159256         PROX1         T/C         0.45         0.42         0.82         0.40         0.17         0.36         0.74           12:102875569         IGF1         G/A         0.16         0.76         0.54         0.62         0.55         0.43         0.10           2:27995781         MRPL33         C/A         0.26         0.11         0.07         0.65         0.43         0.07         0.03           14:100839261         WARS         T/G         0.29         0.045         0.51         0.67         0.60         0.44         0.60           9:139256766         DNLZ         A/G         0.29         0.003         0.13         0.16         0.18         0.74         0.39           10:114756041         TCF7L2         T/A         0.31         3.9E-04         2.5E-05         2.7E-05         0.44         0.09         0.40           7:44235668         GCK         A/G         0.17         2.0E-04         0.003         5.0E-04         0.11         0.09         0.11         0.09         0.13         0.05         0.13         0.05         0.11         0.09         0.11         0.09         0.13         0.05         0.13         0.05         0.13	1:214159256         PROX1         T/C         0.45         0.42         0.82         0.40         0.17         0.36         0.74           12:102875569         IGF1         G/A         0.16         0.76         0.54         0.62         0.55         0.43         0.10           2:27995781         MRPL33         C/A         0.26         0.11         0.07         0.25         0.43         0.01         0.03           14:100839261         WARS         T/G         0.22         0.45         0.51         0.65         0.44         0.60           9:139256766         DNLZ         A/G         0.29         0.003         0.13         0.16         0.18         0.51         0.39           10:114756041         TCF7L2         T/A         0.31         3.9E-04         2.5E-05         2.7E-05         0.44         0.09         0.40           7:44235688         GCK         A/G         0.17         2.0E-04         0.003         5.0E-04         0.11         0.09         0.10           8:9183596         PPP1R3B         A/G         0.09         0.33         0.32         0.05         0.13         0.05         0.13         0.05	425	8:40484239	ZMAT4	1/0	0.12	0.01	0.01	0.78	0.37	0.25	0.35	0.41
12:102875569         IGF1         G/A         0.16         0.76         0.54         0.62         0.43         0.70         0.10           2:27995781         MRPL33         C/A         0.26         0.11         0.07         0.25         0.43         0.07         0.03           14:100839261         WARS         T/G         0.22         0.45         0.51         0.60         0.44         0.60           9:139256766         DNLZ         A/G         0.29         0.003         0.13         0.16         0.16         0.44         0.39           10:114756041         TCF7L2         T/A         0.31         3.9E-04         2.5E-05         2.7E-05         0.44         0.09         0.40           7:44235668         GCK         A/G         0.17         2.0E-04         0.003         5.0E-04         0.11         0.09         0.11         0.09         0.13         0.03         0.05         0.13         0.05         0.13         0.05         0.13         0.05         0.13         0.05         0.09         0.11         0.09         0.11         0.09         0.13         0.03         0.05         0.13         0.05         0.05         0.13         0.05         0.05         0	12:102875569         IGF1         G/A         0.16         0.76         0.54         0.62         0.55         0.43         0.10           2:27995781         MRPL33         C/A         0.26         0.11         0.07         0.05         0.43         0.07         0.03           14:100839261         WARS         T/G         0.22         0.45         0.51         0.06         0.44         0.60           9:139256766         DNLZ         A/G         0.29         0.003         0.13         0.16         0.18         0.51         0.39           10:114756041         TCF7L2         T/A         0.31         3.9E-04         2.5E-05         2.7E-05         0.44         0.09         0.40           7:44235668         GCK         A/G         0.17         2.0E-04         0.003         5.0E-04         0.11         0.09         0.10           8:9183596         PPP1R3B         A/G         0.09         0.33         0.32         0.05         0.13         0.74         0.29	74	1:214159256	PROX1	1/0	0.45	0.42	0.82	0.40	0.17	0.36	0.74	0.15
2:27995781         MRPL33         C/A         0.26         0.11         0.07         0.25         0.43         0.07         0.03           14:100839261         WARS         T/G         0.22         0.45         0.51         0.57         0.06         0.44         0.60           9:139256766         DNLZ         A/G         0.29         0.003         0.13         0.16         0.18         0.51         0.39           10:114756041         TCF7L2         T/A         0.31         3.9E-04         2.5E-05         2.7E-05         0.44         0.09         0.40           7:44235668         GCK         A/G         0.17         2.0E-04         0.003         5.0E-04         0.11         0.09         0.10           8:9183596         PPP1R3B         A/G         0.09         0.33         0.32         0.05         0.13         0.74         0.09	2:27995781         MRPL33         C/A         0.26         0.11         0.07         0.25         0.43         0.07         0.03           14:100839261         WARS         T/G         0.22         0.45         0.51         0.57         0.06         0.44         0.60           9:139256766         DNLZ         A/G         0.29         0.003         0.13         0.16         0.18         0.51         0.39           10:114756041         TCF7L2         T/A         0.31         3.9E-04         2.5E-05         2.7E-05         0.44         0.09         0.40           7:44235668         GCK         A/G         0.17         2.0E-04         0.003         5.0E-04         0.11         0.09         0.10           8:9183596         PPP1R3B         A/G         0.09         0.33         0.32         0.05         0.13         0.74         0.29	7	12:102875569	IGF1	G/A	0.16	0.76	0.54	0.62	0.55	0.43	0.10	0.02
14:100839261         WARS         T/G         0.22         0.45         0.51         0.67         0.06         0.44         0.60           9:139256766         DNLZ         A/G         0.29         0.003         0.13         0.16         0.18         0.51         0.39           10:114756041         TCF7L2         T/A         0.31         3.9E-04         2.5E-05         2.7E-05         0.44         0.09         0.40           7:44235668         GCK         A/G         0.17         2.0E-04         0.003         5.0E-04         0.11         0.09         0.10           8:9183596         PPP1R3B         A/G         0.09         0.33         0.32         0.05         0.13         0.74         0.29	14:100839261         WARS         T/G         0.22         0.45         0.51         0.67         0.06         0.44         0.60           9:139256766         DNLZ         A/G         0.29         0.003         0.13         0.16         0.18         0.51         0.39           10:114756041         TCF7L2         T/A         0.31         3.9E-04         2.5E-05         2.7E-05         0.44         0.09         0.40           7:44235668         GCK         A/G         0.17         2.0E-04         0.003         5.0E-04         0.11         0.09         0.10           8:9183596         PPP1R3B         A/G         0.09         0.33         0.32         0.05         0.13         0.74         0.29	594	2:27995781	MRPL33	C/A	0.26	0.11	0.07	0.25	0.43	0.07	0.03	0.62
9:139256766         DNLZ         A/G         0.29         0.003         0.13         0.16         0.18         0.51         0.39           10:114756041         TCF7L2         T/A         0.31         3.9E-04 <b>2.5E-05 2.7E-05</b> 0.44         0.09         0.40           7:44235668         GCK         A/G         0.17 <b>2.0E-04</b> 0.003 <b>5.0E-04</b> 0.11         0.09         0.10           8:9183596         PPP1R3B         A/G         0.09         0.33         0.32 <b>0.05</b> 0.13         0.74         0.29	9:139256766         DNLZ         A/G         0.29         0.003         0.13         0.16         0.18         0.51         0.39           10:114756041         TCF7L2         T/A         0.31         3.9E-04         2.5E-05         2.7E-05         0.44         0.09         0.40           7:44235668         GCK         A/G         0.17         2.0E-04         0.003         5.0E-04         0.11         0.09         0.10           8:9183596         PPP1R3B         A/G         0.09         0.33         0.32         0.05         0.13         0.74         0.29	347	14:100839261	WARS	1/G	0.22	0.45	0.51	0.57	90.0	0.44	09.0	0.94
10:114756041         TCF7L2         T/A         0.31         3.9E-04         2.5E-05         2.7E-05         0.44         0.09         0.40           7:44235668         GCK         A/G         0.17         2.0E-04         0.003         5.0E-04         0.11         0.09         0.10           8:9183596         PPP1R3B         A/G         0.09         0.33         0.32         0.05         0.13         0.74         0.29	10:114756041         TCF7L2         T/A         0.31         3.9E-04         2.5E-05         2.7E-05         0.44         0.09         0.40           7:44235668         GCK         A/G         0.17         2.0E-04         0.003         5.0E-04         0.11         0.09         0.10           8:9183596         PPP1R3B         A/G         0.09         0.33         0.32         0.05         0.13         0.74         0.29	109	9:139256766	DNLZ	A/G	0.29	0.003	0.13	0.16	0.18	0.51	0.39	0.46
7:44235668         GCK         A/G         0.17         2.0E-04         0.003         5.0E-04         0.11         0.09         0.10           8:9183596         PPP1R3B         A/G         0.09         0.33         0.32         0.05         0.13         0.74         0.29	7:44235668         GCK         A/G         0.17         2.0E-04         0.003         5.0E-04         0.11         0.09         0.10           8:9183596         PPP1R3B         A/G         0.09         0.33         0.32         0.05         0.13         0.74         0.29	292	10:114756041	TCF7L2	T/A	0.31	3.9E-04	2.5E-05	2.7E-05	0.44	0.09	0.40	0.83
8:9183596 <i>PPP1R3B A/</i> G 0.09 0.33 0.32 <b>0.05</b> 0.13 0.74 0.29	8:9183596 <i>PPP1R3B A/</i> G 0.09 0.33 0.32 <b>0.05</b> 0.13 0.74 0.29	517	7:44235668	GCK	A/G	0.17	2.0E-04	0.003	5.0E-04	0.11	0.09	0.10	0.08
	Continued on p. 169	132	8:9183596	PPP1R3B	A/G	0.09	0.33	0.32	0.05	0.13	0.74	0.29	0.05

Table 3—Continued	ontinued					Whites				Blacks	
SNP	Chr.position	A1 Chr.position Closest gene A1/A2 freq	A1/A2	fred fred	P value fructosamine	P value glycated albumin	P value fasting glucose	A1 freq	P value fructosamine	P value glycated albumin	P value fasting glucose
rs560887	2:169763148	G6PC2	1/C	0:30	0.08	0.003	7.3E-05	0.05	0.81	0.58	0.91
rs576674	13:33554302	KL	G/A	0.16	0.45	0.50	0.33	0.61	0.17	0.26	0.11
rs6048205	20:22559601	FOXA2	G/A	0.02	0.79	0.95	20.0	0.18	0.02	0.25	0.05
rs6072275	20:39743905	TOP1	A/G	0.16	0.57	0:30	0.01	0.08	0.13	0.12	0.08
rs6943153	7:50791579	GRB10	1/0	0.31	0.67	0.46	0.16	0.70	0.09	0.77	0.61
rs7034200	9:4289050	ES/79	A/C	0.49	0.19	0.04	0.03	0.61	0.18	0.02	0.11
rs7651090	3:185513392	IGF2BP2	G/A	0.31	0.01	0.03	0.003	0.56	0.32	0.58	0.40
rs7708285	5:76425867	ZBED3	G/A	0.30	0.32	0.64	0.71	0.15	0.56	0.52	0.16
rs780094	2:27741237	GCKR	1/0	0.40	0.05	5.7E-05	1.0E-04	0.18	0.75	96.0	06:0
rs7944584	11:47336320	MADD	T/A	0.27	0.56	0.76	0.05	0.04	0.98	0.38	0.77
rs9368222	6:20686996	CDKAL1	A/C	0.27	0.19	0.09	0.27	0.20	96.0	0.80	0.68
freq, frequen glycated alb	icy. Candidate SN umin, $P < 3.0  imes$	freq, frequency. Candidate SNPs selected from NHGRI database b glycated albumin, $P < 3.0 \times 10^{-4}~(0.05/(2^241))$ , and $P$ values t	NHGRI	databa:   P value	se based on pre es that reach n	based on previous genome-wide significant associations. P values that reach study-value thominal significance ( $P<0.05$ ) for fasting glucose are in boldface type.	significant association $< 0.05$ ) for fasting	ns. P valt glucose	ues that reach stu are in boldface t	freq, frequency. Candidate SNPs selected from NHGRI database based on previous genome-wide significant associations. P values that reach study-wide significance for fructosamine and glycated albumin, $P < 3.0 \times 10^{-4}$ (0.05/(2*2*41)), and P values that reach nominal significance ( $P < 0.05$ ) for fasting glucose are in boldface type.	or fructosamine and

in the same direction in blacks and whites (Table 4 and Supplementary Table 7), and 43 had consistent direction with the discovery cohort in whites. Five SNPs (11%) demonstrated a study-wide significant association with fructosamine or glycated albumin in whites. All variants associated with multiple glycemic biomarkers had effects in the same direction.

## **Percent Variance Explained**

SNPs associated with fasting glucose (N=41) (Table 3) explained 1.4% of the variance in fructosamine, 3.2% of the variance in percent glycated albumin, and 1.9% of the variance in total glycated albumin among whites. Taking SNPs associated with serum albumin from the GWAS catalog explained 0.4% of the variance of fructosamine, 1.1% of the variance of percent glycated albumin, and 0.7% of the variance of total glycated albumin among the white sample.

## DISCUSSION

We identified four SNPs significantly associated with fructosamine and glycated albumin among either whites or blacks, one which replicated in a second cohort and three not previously associated with glycemic traits. Several known fasting glucose and HbA<sub>1c</sub> SNPs were significantly associated with fructosamine or glycated albumin.

Among whites, rs1260326 was associated with percent glycated albumin. This variant reflects the same signal associated with type 2 diabetes and fasting glucose: it is in perfect LD with a known type 2 diabetes variant  $(r^2 = 1 \text{ among } 1000 \text{ Genomes phase } 3 \text{ Europeans with}$ rs145819220, from a recent large type 2 diabetes GWAS [38]) and in strong LD with a known fasting glucose variant ( $r^2 = 0.91$  with rs780094 [37,38]). rs1260326 is located in glucokinase (hexokinase 4) regulator (GCKR), which encodes a regulatory protein primarily active in the liver that inhibits glucokinase (GCK), the enzyme in the first step of glycolysis and involved in converting glucose to glycogen for storage. GCK is considered a glucose sensor that helps maintain glucose homeostasis. The GCKR protein product inhibits the activity of GCK, increasing serum glucose levels. GCKR is an established type 2 diabetes gene (39-41) and is associated with multiple other traits including kidney disease, triglyceride levels, and Crohn disease (42-44). Thus, this variant likely represents part of a glycemic pathway, but it is interesting that in our study it is only significantly associated with one measure of hyperglycemia, approached significance with fasting glucose (although controlling for fasting glucose score made this variant nonsignificant) and total glycated albumin, but is not associated with fructosamine or HbA<sub>1c</sub>, given the moderate to strong correlations and genetic correlations among the biomarkers (Supplementary Tables 5 and 8). That GCKR is primarily expressed in the liver rather than the pancreas (45,46) aligns with the finding of association with fasting glucose, which measures hepatic glucose output. Albumin is also produced by the liver, while erythrocytes

glycated albumin in ARIC	
inown genetic determinants and fructosamine and percent	
Table 4—Significance of associations between HbA <sub>1c</sub> k	

		ĺ																																93
	P value	HDA <sub>1c</sub>	0.585	0.503	0.899	0.222	0.485	0.989	0.734	0.074	0.184	0.475	999.0	0.146	0.772	0.656	0.514	0.802	0.689	0.890	0.146	0.260	0.160	0.596	0.632	0.297	0.961	0.246	0.910	0.244	0.361	0.602	0.181	Continued on p. 1693
Blacks	P value glycated	albumin	0.455	0.142	0.529	0.035	0.354	0.176	0.950	0.003	0.220	0.748	0.853	0.826	0.854	0.728	0.176	0.524	0.232	0.755	0.670	0.270	0.349	0.763	0.824	0.745	0.167	0.142	0.134	0.097	0.461	0.921	0.029	Contin
	P value	Iructosamine	0.661	0.221	0.808	0.134	0.067	0.309	0.788	0.002	0.812	0.180	0.829	0.500	0.220	0.471	0.065	0.604	0.403	0.396	0.846	0.533	0.177	0.293	0.813	0.853	0.111	0.050	0.086	0.088	0.274	0.889	0.073	
	A1	lied	0.24	60.0	0.45	0.07	0.36	60.0	90.0	0.16	0.05	0.36	0.84	0.21	0.30	0.31	0.11	60.0	0.24	0.07	0.01	0.88	0.42	0.19	0.63	0.04	0.22	69.0	0.24	0.11	0.46	0.10	0.72	
	P value	прА <sub>1с</sub>	0.052	0.008	1.1E-06	9000	0.055	0.010	0.228	0.034	N A	0.702	0.358	0.001	0.031	2.7E-07	0.131	0.027	5.0E-04	1.8E-04	0.001	0.123	0.002	0.007	0.002	0.511	90-36-6	1.0E-04	0.125	5.7E-05	0.018	5.8E-06	0.010	
Whites	P value glycated	alburnin	0.048	0.032	0.065	0.003	0.229	8.2E-05	0.078	0.001	NA	0.844	0.294	0.930	0.662	9.3E-05	0.017	0.152	0.167	3.2E-05	0.128	0.198	0.938	0.019	0.879	0.434	0.792	0.248	0.002	0.003	0.515	0.263	0.350	
	P value	ructosamine	0.034	0.571	0.452	0.001	0.011	0.005	0.005	0.070	ΑN	0.861	0.732	0.765	0.800	0.016	0.545	0.309	0.577	1.7E-04	0.337	0.390	0.321	0.008	0.567	0.444	0.714	0.586	3.3E-04	2.0E-04	0.126	0.190	0.264	
	A1	lred	0.31	0.48	0.26	0.28	0.35	0.32	0.16	0.23	0.00	0.43	0.39	0.47	0.32	0.22	0.41	0.14	0.21	0.23	90.0	0.16	0.10	0.18	0.48	0.21	0.27	0.12	0.42	0.17	0.24	0.07	0.46	
	· ·	AI/AZ	1/C	G/A	G/A	G/C	C	G/A	A/G	G/A	G/C	G/A	5	A/C	A/G	T/C	¥	5	AG	5	A/G	A/G	1/0	G/A	G/T	G/T	1/0	G/A	1/C	A/G	A/G	G/T	G/A	
	Closest	dene	<b>FN3KRP</b>	ATXN2	HK1	MTNR1B	ITFG3	SLC30A8	ARAP1	ADCY5	SOX30	C6orf183	FOXN2	RP1	FREM3	G6PC2	FTO	ATAD2B	MYO9B	TCF7L2	HFE	HFE	PHB2	MTAP	SENP1	CERS2	SPTA1	ATP11A	GCK	GCK	ANK1	HK1	TMPRSS6	
		Cur:position	17:80685533	12:111910219	10:71091013	11:92708710	16:293562	8:118185733	11:72432985	3:123065778	5:157055491	6:109562035	2:48414735	12:48409054	4:144659795	2:169757354	16:53803574	2:24021231	19:17256523	10:114752503	6:26093141	6:26107463	12:7075882	9:22132076	12:48499131	1:150940625	1:158585415	13:113351662	7:44247258	7:44235668	8:41630405	10:71089843	22:37469591	
	Ç	ANIO L	rs1046896	rs10774625	rs10823343	rs10830963	rs11248914	rs11558471	rs11603334	rs11708067	rs11954649	rs11964178	rs12621844	rs12819124	rs13134327	rs1402837	rs1558902	rs17509001	rs17533903	rs17747324	rs1800562	rs198846	rs2110073	rs2383208	rs2408955	rs267738	rs2779116	rs282587	rs3824065	rs4607517	rs4737009	rs4745982	rs4820268	

SNP         Chrosation         41         P value glycated plumin         And plumin         P value glycated plumin         And plumin	Table 4—Continued	ontinued					Whites				Blacks	
2:169763148         G6PCZ         T/C         0.080         0.003         0.003         0.001         0.13         0.031         0.583         0.887	SNP	Chr:position	Closest	A1/A2	A1 freq	P value fructosamine	P value glycated albumin	P value HbA <sub>1c</sub>	A1 freq	P value fructosamine	P value glycated albumin	P value HbA₁c
9:136154168         ABO         C7T         0.238         0.268         0.034         0.001         0.130         0.210         0.487           6:139840693         C7TED2         A/C         0.46         0.514         0.535         0.063         0.61         0.323         0.605           8:41549194         ANKT         C/T         0.48         0.514         0.78         0.047         0.047         0.047           8:42383084         SLC20A2         A/G         0.39         0.256         0.873         0.015         0.48         0.514         0.557           9:91503236         C90r47         G/C         0.74         0.499         0.765         0.001         0.26         0.028         0.045         0.055           17:76122078         TMC         G/A         0.74         0.75         0.769         0.719         0.799 <td>rs560887</td> <td>2:169763148</td> <td>G6PC2</td> <td>1/C</td> <td>0:30</td> <td>0.080</td> <td>0.003</td> <td>0.003</td> <td>0.95</td> <td>0.811</td> <td>0.583</td> <td>0.861</td>	rs560887	2:169763148	G6PC2	1/C	0:30	0.080	0.003	0.003	0.95	0.811	0.583	0.861
6:138840693         CITED2         A/C         0.46         0.514         0.635         0.063         0.61         0.323         0.605           8:41549194         ANK1         C/T         0.03         0.979         0.486         4.3E-04         0.27         0.077         0.047           8:42383084         SLC20A2         A/G         0.39         0.256         0.873         0.015         0.048         0.514         0.047         0.047           9:91503236         C90r47         G/C         0.07         0.499         0.785         0.019         0.56         0.058         0.057         0.055           17:76122078         TMC6         G/T         0.180         0.705         0.784         0.26         0.059         0.	rs579459	9:136154168	ABO	CY	0.23	0.268	0.340	0.001	0.13	0.210	0.487	0.600
8.41549194         ANKT         C/T         0.03         0.979         0.486         4.3E-04         0.277         0.047         0.047           8.42383084         5LC20A2         A/G         0.39         0.256         0.873         0.015         0.48         0.514         0.557           9:91503236         C90r47         G/C         0.07         0.499         0.765         0.001         0.26         0.026         0.005           3:12267648         SYNZ         G/A         0.43         0.775         0.189         0.094         0.27         0.095         0.005         0.018         0.056         0.005         0.0	rs592423	6:139840693	CITED2	A/C	0.46	0.514	0.535	0.063	0.61	0.323	0.605	0.333
8:42383084         SLC20A2         A/G         0.39         0.256         0.015         0.015         0.514         0.557           9:91503236         C90r47         G/C         0.07         0.499         0.765         0.001         0.26         0.028         0.005           3:12267648         SYN2         G/A         0.43         0.705         0.189         0.181         0.26         0.029         0.005         0.018         0.059         0.005         0.018         0.059         0.005         0.018         0.059         0.059         0.018         0.059         0.059         0.035         0.059         0.059         0.048         0.059         0.035         0.059         0	rs6474359	8:41549194	ANK1	CY	0.03	0.979	0.486	4.3E-04	0.27	0.077	0.047	0.879
9:91503236         Cyorf47         G/C         0.07         0.499         0.765         0.001         0.26         0.028         0.005           3:12267648         SYNZ         G/A         0.43         0.705         0.385         0.181         0.36         0.974         0.959           17:76122078         TMC6         C/T         0.13         0.077         0.180         0.109         0.092         0.42         0.860         0.361           6:20679709         CDKAL1         G/A         0.27         0.180         0.094         0.29         0.42         0.897         0.997           3:170724883         SLC2A2         C/T         0.4         0.591         0.804         0.56         0.492         0.56         0.492         0.56         0.492         0.56         0.492         0.56         0.492         0.56         0.992         0.254           1:158626378         SPTA1         T/C         0.26         0.482         0.300         0.687         0.692         0.297         0.583           13:114542868         GAS6         A/G         0.7         0.248         0.870         0.780         0.992         0.297         0.297           17:27183104         ERAL1	rs6980507	8:42383084	SLC20A2	A/G	0.39	0.256	0.873	0.015	0.48	0.514	0.557	0.663
3:12267648         SYNZ         G/A         0.43         0.705         0.385         0.181         0.36         0.974         0.959           17:76122078         TMC6         C/T         0.13         0.077         0.109         0.094         0.13         0.480         0.361           6:20679709         TMC6         C/T         0.18         0.077         0.094         0.092         0.42         0.856         0.997           1:88853729         C/DT1         C/T         0.44         0.591         0.804         0.56         0.492         0.56         0.492         0.232         0.232           1:158626378         SPTA1         T/C         0.24         0.803         0.492         5.66-06         0.30         0.992         0.256           1:3:1452858         GAS6         A/G         0.26         0.482         0.300         0.687         0.24         0.902         0.833           3:49382925         USP4         A/G         0.71         0.240         0.870         0.058         0.095         0.297         0.080	rs7040409	9:91503236	C9orf47	G/C	0.07	0.499	0.765	0.001	0.26	0.028	0.005	0.115
17:76122078         TMC6         C/T         0.13         0.077         0.109         0.094         0.13         0.480         0.361           6:20679709         CDKAL1         G/A         0.27         0.180         0.094         0.292         0.42         0.856         0.997           3:170724883         SLC2A2         C/T         0.30         5.4E-05         6.1E-05         0.010         0.29         0.232         0.232         0.232           16:88853729         CD71         C/T         0.44         0.591         0.804         0.56         0.392         0.554           11:158626378         SPTA1         T/C         0.25         0.803         0.492         5.6E-06         0.30         0.092         0.256           13:114542858         GAS6         A/G         0.27         0.482         0.300         0.780         0.297         0.297           3:49382925         USP4         A/G         0.21         0.307         0.993         0.058         0.66         0.252         0.080	rs7616006	3:12267648	SYN2	G/A	0.43	0.705	0.385	0.181	0.36	0.974	0.959	0.836
6:20679709         CDKAL1         G/A         0.27         0.180         0.094         0.292         0.42         0.856         0.997           3:170724883         SLC2A2         C/T         0.30 <b>5.4E-05 6.1E-05 0.010</b> 0.29         0.232         0.239           16:88853729         CD71         C/T         0.44         0.591         0.804         0.56         0.492         0.554           11:158626378         SP7A1         T/C         0.25         0.482         0.300         0.092         0.226           13:114542858         GASG         A/G         0.17         0.240         0.870         0.780         0.297         0.297           3:49382925         USP4         A/G         0.71         0.307         0.058         0.056         0.66         0.297         0.080	rs761772	17:76122078	1MC6	CY	0.13	0.077	0.109	600.0	0.13	0.480	0.361	0.861
3:170724883         SLC2A2         CT         0.30         5.4E-05         6.1E-05         0.010         0.29         0.232         0.239           16:88853729         CD71         CT         0.44         0.591         0.804         0.56         0.30         0.92         0.554           11:158626378         SPTA1         T/C         0.25         0.803         0.492         5.6E-06         0.30         0.092         0.256           13:114542858         GAS6         A/G         0.17         0.240         0.870         0.780         0.297         0.297           3:49382925         USP4         G/A         0.21         0.307         0.058         0.66         0.252         0.080	rs7756992	6:20679709	CDKAL1	G/A	0.27	0.180	0.094	0.292	0.42	0.856	0.997	0.995
16:88853729         CDT1         C/T         0.44         0.591         0.046         0.56         0.492         0.554           1:158626378         SPTA1         T/C         0.25         0.803         0.492         5.6E-06         0.30         0.092         0.226           13:114542858         GAS6         A/G         0.24         0.482         0.300         0.687         0.24         0.902         0.833           3:49382925         USP4         A/G         0.17         0.240         0.780         0.09         0.297         0.080           17:27183104         ERAL1         G/A         0.21         0.303         0.993         0.058         0.66         0.252         0.080	rs8192675	3:170724883	SLC2A2	CY	0:30	5.4E-05	6.1E-05	0.010	0.29	0.232	0.239	0.024
1:158626378         SPTA1         T/C         0.25         0.803         0.492         5.6E-06         0.30         0.092         0.226           13:114542858         GAS6         A/G         0.26         0.482         0.300         0.687         0.24         0.902         0.833           3:49382925         USP4         A/G         0.17         0.240         0.870         0.780         0.09         0.297         0.297           17:27183104         ERAL1         G/A         0.21         0.307         0.993         0.058         0.66         0.252         0.080	rs837763	16:88853729	CD11	CY	0.44	0.591	0.804	0.046	0.56	0.492	0.554	0.533
13:114542858         GAS6         A/G         0.26         0.482         0.300         0.687         0.24         0.902         0.833           3:49382925         USP4         A/G         0.17         0.240         0.870         0.780         0.09         0.297         0.297           17:27183104         ERAL1         G/A         0.21         0.307         0.993         0.058         0.66         0.252         0.080	rs857691	1:158626378	SPTA1	1/C	0.25	0.803	0.492	5.6E-06	0.30	0.092	0.226	0.894
3:49382925         USP4         A/G         0.17         0.240         0.870         0.780         0.09         0.297         0.297           17:27183104         ERAL1         G/A         0.21         0.307         0.993         0.058         0.66         0.252         0.080	rs9604573	13:114542858	GAS6	A/G	0.26	0.482	0.300	0.687	0.24	0.902	0.833	0.425
17:27183104 <i>ERAL1</i> G/A 0.21 0.307 0.993 0.058 0.66 0.252 0.080	rs9818758	3:49382925	USP4	A/G	0.17	0.240	0.870	0.780	0.09	0.297	0.297	0.642
	rs9914988	17:27183104	ERAL1	G/A	0.21	0.307	0.993	0.058	99.0	0.252	0.080	0.342

freq, frequency. Candidate SNPs selected from NHGRI database based on previous genome-wide significant associations. P values that reach study-wide significance for fructosamine and glycated albumin,  $P < 2.7 \times 10^{-4}$  (0.05/(2\*2\*46)), and P values that reach nominal significance (P < 0.05) for HbA<sub>1c</sub> are in boldface type.

and hemoglobin are not likely affected by liver function, thus perhaps hepatic-specific genetic factors would be more likely to associate with percent glycated albumin levels than with  $HbA_{1c}$ . It is also possible that  $HbA_{1c}$ , affected by other glucose-altering factors, may mask the effect of rs1260326 on *GCKR*. Adjustment for serum albumin may explain the association with percent glycated albumin but not fructosamine.

We also identified several variants of potential interest that were significant in ARIC but lacked replication. Among whites, rs34459162, in RCN3, was associated with fructosamine and total glycated albumin. RCN3 encodes reticulocalbin 3, an EF-hand calcium binding domain (47). This SNP was not associated with serum albumin in our analysis, but a SNP in perfect LD with rs34459162, rs2280401, was associated with total protein in a Japanese population (48) and serum albumin in an East Asian population (49), indicating a possible impact on fructosamine and glycated albumin through nonglycemic pathways. Among blacks, we found two novel variants: rs2438321 (intergenic and closest to CNTN5, which encodes a glycosylphosphatidylinositol-anchored neuronal membrane protein, a member of the immunoglobulin superfamily and the contactin family) associated with fructosamine and rs59443763 (PRKCA, which encodes protein kinase C alpha, ubiquitous in cellular processes) associated with percent glycated albumin at a genome-wide level of significance. There is no prior literature on either of these as potential glycemic loci in diabetes. While we had sufficient power to replicate the results for whites in CARDIA (Supplementary Table 2), we had low power among blacks, which may be why these SNPs did not replicate. These variants became nonsignificant after excluding undiagnosed diabetes, which may be due to the greater number of individuals with undiagnosed diabetes among blacks than whites. Blacks had higher values of glycemic biomarkers, thus removing case subjects with undiagnosed diabetes could have had a greater impact on associations among blacks than whites. These variants should be evaluated in larger African ancestry data sets as they become available. rs34459162, rs2438321, and rs59443763 are of potential interest, but as these SNPs currently lack replication, we cannot rule out false positive results.

Results varied by ancestry for the SNPs available in both blacks and whites: neither SNP was significant in both blacks and whites, and meta-analyses results were nonsignificant. While this may partially be explained by differing allele frequencies (rs1260326: 0.41 in whites, 0.14 in blacks; rs2438321: 0.24 in whites, 0.11 in blacks), a differential effect by ancestry on fructosamine and glycated albumin is also possible. This may be particularly true for rs2438321, where the direction of effect differs across ancestries.

In addition to investigating fructosamine and glycated albumin individually, comparing to traditional glycemic markers (fasting glucose and  $HbA_{1c}$ ) can help to clarify the

biological pathways involved in diabetes. Fasting glucose-related SNPs explained almost twice the variance of percent glycated albumin than that of fructosamine. This may reflect the adjustment for serum albumin with percent glycated albumin and not with fructosamine, allowing percent glycated albumin levels to be influenced more by glucose levels and less by albumin levels. However, albumin SNPs also explained more variance of percent glycated albumin than that of fructosamine or total glycated albumin. Given the small percentages, it is difficult to draw first conclusions from these results.

Only five  $HbA_{1c}$  variants were significantly associated with fructosamine or glycated albumin. This is consistent with the findings that the majority of  $HbA_{1c}$  variants are related to erythrocyte and hemoglobin factors that we would not expect to be related to fructosamine or glycated albumin. Many associations of fructosamine or glycated albumin with  $HbA_{1c}$  SNPs or fasting glucose SNPs were present in whites but not blacks. This is not surprising given that the SNPs were originally detected in whites and that our sample size was larger for whites, with corresponding higher power to detect moderate associations. Not all of the previously discovered SNPs for fasting glucose and  $HbA_{1c}$  replicated for those outcomes in our sample, but this again may have to do with lack of power.

We found that both glycemic and nonglycemic genetic factors influenced fructosamine and glycated albumin levels. We identified a likely glycemic variant in a gene associated with type 2 diabetes (GCKR), supporting its role in diabetes biology, and a likely nonglycemic variant in a gene (RCN3) that may reflect the biology of a biomarker (i.e., influencing amount of serum protein available to be glycated) rather than the biology of type 2 diabetes. This contribution of glycemic and nonglycemic variants is similar to the pattern of genetic contribution to HbA<sub>1c</sub>, for which the majority of genetic variants are nonglycemic (18,19). In our study, previously identified nonglycemic variants (18-20) explained 3.4% of the variance in HbA<sub>1c</sub> and the glycemic variants explained 2.1% (Supplementary Table 9). Despite the previous studies having much larger sample sizes (and thus more power to detect associations with HbA<sub>1c</sub>), the percent variance explained we found for fructosamine (0.6% by likely nonglycemic rs34459162) and glycated albumin (0.3% by likely glycemic rs1260326) was of a similar magnitude. Both Soranzo et al. (18) and Chen et al. (19) found that taking nonglycemic variants into account modestly impacted diabetes reclassification, and Wheeler et al. (20) found a more substantial effect. Given that that future larger studies on fructosamine and glycated albumin will likely reveal other significant variants, it will be important to determine whether the effect of nonglycemic variants is substantial enough to impact the clinical interpretation of fructosamine and glycated albumin.

A major limitation of this study was the limited sample size, particularly the smaller sample size in blacks. The differences in ancestries make replication of results difficult, particularly if allele frequencies differ, and warrant more studies focused on multiethnic populations. Also, the lack of an available SNP or proxy for rs59443763 in CARDIA, possibly due to the imputation reference panel (HapMap Phase II), impeded our ability to evaluate replication of this finding. In addition, the sample size for our replication cohort was much smaller than our discovery cohort, limiting our power to replicate the significant ARIC findings in blacks.

In summary, through GWAS in a community-based population of blacks and whites, we identified and replicated two significant variants associated with fructosamine and/or glycated albumin, one of which was novel. These variants map into a likely glycemic, known diabetes gene and a likely nonglycemic gene. This highlights the utility of examining genetics of diabetes biomarkers both for providing insight into the pathophysiology of diabetes and for better understanding glucose-independent influences on measures of hyperglycemia.

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**Author Contributions.** S.J.L. and N.M.M. wrote the manuscript. M.L. and A.S.B. performed data analysis and reviewed and edited the manuscript. K.E.N., H.M., A.M., A.P.C., J.S.P., E.B., R.S., L.J.R.-T., and J.C. reviewed and edited the manuscript. P.D., A.K., and E.S. contributed to discussion, provided guidance, and reviewed and edited the manuscript. S.J.L. and M.L. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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