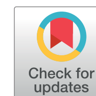

An Expanded Genome-Wide Association Study of Fructosamine Levels Identifies *RCN3* as a Replicating Locus and Implicates *FCGRT* as the Effector Transcript

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Fructosamine is a measure of short-term glycemic control, which has been suggested as a useful complement to glycated hemoglobin (HbA_{1c}) for the diagnosis and monitoring of diabetes. To date, a single genome-wide association study (GWAS) including 8,951 U.S. White and 2,712 U.S. Black individuals without a diabetes diagnosis has been published. Results in Whites and Blacks yielded different association loci, near *RCN3* and *CNTN5*, respectively. In this study, we performed a GWAS on 20,731 European-ancestry blood donors and meta-analyzed our results with previous data from U.S. White participants from the Atherosclerosis Risk in Communities (ARIC) study (N_{meta} = 29,685). We identified a novel association near *GCK* (rs3757840, β_{meta} = 0.0062; minor allele frequency [MAF] = 0.49; P_{meta} = 3.66 × 10^{-8}) and confirmed the association near *RCN3* (rs113886122, β_{meta} = 0.0134; MAF = 0.17; P_{meta} = 5.71 × 10^{-18}). Colocalization analysis with whole-blood expression quantitative trait loci data suggested *FCGRT* as the effector transcript at the *RCN3* locus. We further showed that fructosamine has low heritability (h2 = 7.7%), has no significant genetic correlation with HbA_{1c} and other glycemic traits in individuals without a diabetes diagnosis (P > 0.05), but has evidence of shared genetic etiology with some anthropometric traits (Bonferroni-corrected P < 0.0012). Our results broaden knowledge of the genetic architecture of fructosamine and prioritize *FCGRT* for downstream functional studies at the established *RCN3* locus.

Fructosamine is a measure of total glycated proteins in serum. Since the most abundant serum protein is albumin, fructosamine predominately reflects glycation of albumin (1). In contrast to glycated hemoglobin (HbA_{1c}), which reflects average glycemia during the preceding 3 months, fructosamine measures short-term glycemic control (from 2 to 3 weeks), reflecting the shorter turnover time of serum proteins (1). As it is independent of hemoglobin, fructosamine levels are not affected by red cell turnover or characteristics of hemoglobin, making it a viable alternative to HbA_{1c} to monitor glycemic control in the presence of anemia or a hemoglobinopathy (1). Another important difference is that whereas fructosamine reflects levels of

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extracellular glucose, HbA_{1c} is a measure of intracellular glycation. Determinants of these two measurements may reflect differences in glycation in the two different environments (2). Despite its potential advantages and its association with diabetes incidence, retinopathy, and chronic kidney disease (CKD), independently of baseline fasting glucose (FG) and HbA_{1c} (1,3), fructosamine has not been widely used as a measure of glucose control (4).

To date, a single study has examined the single nucleotide polymorphism–based heritability of fructosamine, yielding an h^2 estimate of ~13% (5). A fructosamine genome-wide association study (GWAS) performed on 8,951 U.S. White individuals ($N_{\text{discovery}}$ = 7,647) and 2,712 Black individuals ($N_{\text{discovery}}$ = 2,104) without a diabetes diagnosis found an association in Whites near *RCN3* (rs34459162, $P_{discovery}$ =5.3 × 10^{-9}) and an association near *CNTN5* (rs2438321, $P_{discovery}$ = 6.2 × 10^{-9}) in Blacks but neither variant replicated in additional samples ($N_{\text{replication}}$ = 1,304 and $N_{\text{replication}}$ = 608, respectively). This study also demonstrated that, despite some evidence ($P < 2.7 \times 10^{-4}$) of association with three established FG and/or HbA_{1c} loci (*TCF7L2*, *GCK*, and *SLC2A2*), there was no significant ($P > 0.05$) genetic correlation of fructosamine with FG or HbA_{1c}.

In this study, we aimed to gain further insight into the genetic architecture of fructosamine by performing a GWAS in 20,731 European-ancestry blood donors from the INTERVAL cohort (6). To increase power for novel locus discovery, we combined our results with association statistics from U.S. White participants from the study by Loomis et al. (7) in a meta-analysis (N_{meta} = 29,685). Lastly, we explored the heritability of the trait and its genetic relationship with other glycemic and nonglycemic traits to establish the degree of shared genetic influences.

RESEARCH DESIGN AND METHODS

We conducted a GWAS for fructosamine using the INTERVAL cohort (6) and then meta-analyzed our results with those of U.S. White participants from the previously published Atherosclerosis Risk in Communities (ARIC) Study (7). The INTERVAL cohort consists of 47,394 blood donors in the U.K. (6). The ARIC Study consists of 15,792 participants recruited from four U.S. communities (8).

All participants from the INTERVAL cohort were genotyped using the Affymetrix UK Biobank Axiom Array and imputed using a combined UK10K-1000G phase III imputation panel (9) and those from ARIC were genotyped using the Affymetrix 6.0 array and imputed separately by race using the 1000G Project phase I reference panel (7). Genotype quality control for INTERVAL has been previously described in Astle et al. (9). Briefly, samples with poor signal intensity (dish quality control <0.82) or low call rate (<97%) were excluded. Duplicated, contaminated, and non-European samples were also excluded. Variants with low call rate (<95%) and those with cluster statistics indicating poor quality genotyping or hard-to-call multiallelic variants were excluded. Additionally, before imputation, variants were removed using the following filters: *1*) Hardy-Weinberg equilibrium $P < 5 \times 10^{-6}$; *2*) call rate <99% over the genotyping batches in which the variant did not fail; and *3*) global call rate <75% (over 10 genotyping batches). After imputation, the total number of variants was 87,696,910. In ARIC, samples with high missingness (>5%), sex mismatch, discordance with previous TaqMan assay genotypes, genetic outliers, and relatedness were excluded (9). Low frequency variants (minor allele frequency [MAF] <5%) and those with imputation quality <0.8 were excluded, resulting in 5,446,889 variants (7).

Phenotyping for the INTERVAL cohort was performed by Star-SHL laboratory (https://www.star-shl.nl/), and fructosamine was measured on 28,310 INTERVAL cohort participants using a colorimetric assay (Roche/Hitachi Modular P analyzer system). We performed phenotype quality control in R (10) to prepare the data for association analysis. After adjusting for relevant biometric and technical variables (sex, donation center, height, weight, processing date, number of donations, and attendance date), values were transformed on the natural log scale in order to match the approach taken by Loomis et al. (7). After removal of participants on glucose-lowering medication and phenotype quality control, we kept 20,731 participants with fructosamine and genotype data. Fructosamine in ARIC was measured using a Roche Modular P800 system from serum collected at visit 2.

BOLT-LMM (11) was used to run genome-wide association analysis on 19,100,024 variants with MAF >0.1% and INFO score >0.4. Linkage disequilibrium (LD) score regression results showed no signs of inflation, so no genomic correction was performed (LD intercept = 1.01). Summary statistics for ARIC White participants from Loomis et al. (7) were obtained from the authors. We then performed inverse variance-weighted meta-analysis using a fixed-effects model in METAL (12). In total, 5,200,018 were included in the meta-analysis. Variants were clumped into the same locus if they were within 250 kb of the lead variant and if $r^2 > 0.1$. Clumping was performed as implemented in PLINK (13). Variants were declared as genome-wide significant if they met the standard genome-wide significance threshold ($P < 5 \times 10^{-8}$). To identify potential effector transcripts at the *RCN3* locus, expression data from Genotype-Tissue Expression (GTEx) v7 (https://gtexportal.org/) (14) were used to discover colocalized expression quantitative trait locis (eQTLs) in whole blood. For this purpose, we used coloc (15), a software package that calculates the probability of two phenotypes sharing a causal variant in a region by performing approximate Bayes factor colocalization analysis. Protein-coding genes within 1 Mb of the lead variant in the *RCN3* locus were tested for colocalization.

LD score regression (16) was used to establish the heritability of the trait. Genetic correlation analyses with

glycemic traits, hematological traits, anthropometric traits, and kidney diseases/traits (Supplementary Table 1) were performed using LD Hub (17). Power calculation for genetic correlation analyses was done using the GCTA-GREML Power Calculator (18).

Data and Resource Availability

Summary statistics from the genome-wide association analysis in INTERVAL will be available from the GWAS catalog upon publication under accession GCST90017143.

RESULTS

Genome-wide association analysis of fructosamine in 20,731 blood donors from INTERVAL (19,100,024 variants; MAF >0.1%) yielded two genome-wide significant ($P < 5 \times 10^{-8}$) loci. The *ABCB11* locus (rs853777, $\beta = -0.009$ [95% CI -0.013 to -0.007]; MAF = 0.35; $P = 8.8 \times 10^{-9}$) previously associated with HbA_{1c} and FG (19) and the *RCN3* locus (rs111476047, $\beta = 0.013$ [95% CI 0.009–0.017]; MAF = 0.21; $P = 2.1 \times 10^{-11}$) associated with fructosamine in Loomis et al. (7) (Table 1). Next, to increase power for additional locus discovery, we performed genome-wide meta-analysis of our data set with that of White participants from Loomis et al. (7). Following meta-analysis (Table 1 and Supplementary Figs. 1–4), two loci were genome-wide significant: *RCN3* (rs113886122, effect allele = C; $\beta = 0.013$ [95% CI 0.010–0.017]; MAF = 0.17; $P_{meta} = 5.71 \times 10^{-18}$) and *GCK* (rs3757840, effect allele = T; $\beta = 0.006$ [95% CI 0.004–0.008]; MAF = 0.49; $P_{meta} = 3.66 \times 10^{-8}$), another established glycemic trait locus (19). In contrast, the association at the *ABCB11* locus was no longer genome-wide significant ($P_{meta} = 8.50 \times 10^{-7}$) due to lack of supporting evidence for association at this locus in ARIC (rs853777, effect allele = T; $\beta = -0.002$ [95% CI -0.005 to 0.001]; $P = 0.17$) (Table 1).

While *GCK* is known to be the effector transcript at this locus (20), little is known about the *RCN3* locus and its relationship with fructosamine. We therefore sought to explore if eQTL information could point toward potential effector transcripts at this locus. Of 42 protein-coding genes within 1 Mb of the lead signal (rs113886122), only the *FCGRT* eQTL in whole blood displayed convincing evidence of a shared causal variant with same direction of effect (posterior probability 97.7%) (Supplementary Table 2), suggesting it is the likely effector transcript at this locus (Fig. 1).

To estimate the heritability of fructosamine, we next used LD score regression to estimate its heritability explained by common genetic variation (MAF >0.05 in EUR) and to quantify the degree of genetic correlation of fructosamine with other glycemic-related traits. Heritability was estimated to be 7.7% (95% CI 3.6–11.9). Genetic correlation results with anthropometric, glycemic, kidney, and blood cell traits (Supplementary Table 1) showed evidence of moderate negative genetic correlation (rg) (Bonferroni-corrected threshold $P < 0.0012$) with waist-to-hip

Table 1—Genome-wide significant loci in INTERVAL GWAS and/or meta-analysis

						INTERVAL			ARIC			Meta-analysis			
SNP	Chr	MAF	Position	A1	A2	β	SE	*P* value	β	SE	*P* value	β	SE	*P* value	Nearest gene
rs113886122	19	0.17	50044741	c	g	0.0139	0.0021	4.90×10^{-11}	0.0129	0.0023	1.70×10^{-8}	0.0134	0.0016	5.71×10^{-18}	*RCN3* (intron)
rs853777	2	0.35	169812217	c	t	−0.0099	0.0017	8.80×10^{-9}	−0.0022	0.0016	1.70×10^{-1}	−0.0058	0.0012	8.50×10^{-7}	*ABCB11* (intron)
rs3757840	7	0.49	44231216	t	g	0.0049	0.0016	1.80×10^{-3}	0.0075	0.0016	2.80×10^{-6}	0.0062	0.0011	3.66×10^{-8}	*GCK* (upstream)

β values are presented as log values of fructosamine in μmol/L. A1, trait increasing allele; A2, other allele; Position, position in hg19; SNP, single nucleotide polymorphism.

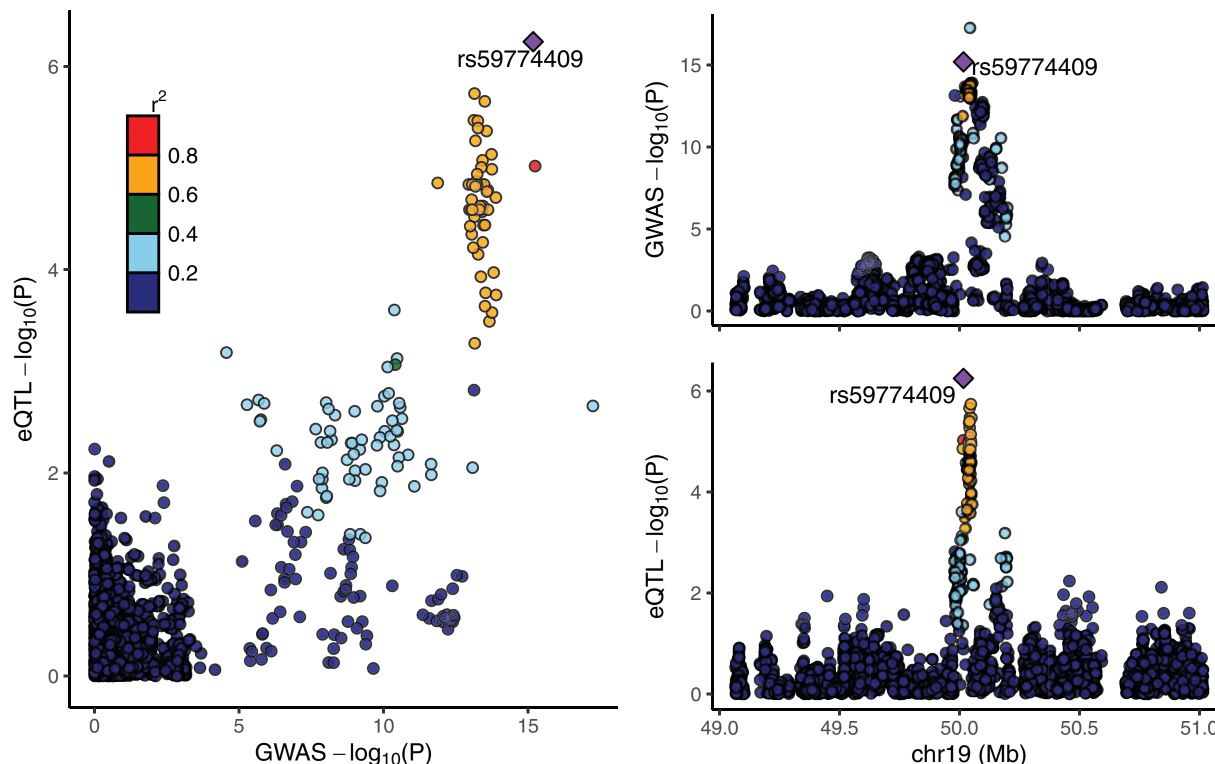

Figure 1—LocusCompareR (29) plot highlighting *FCGRT* region. eQTL refers to expression data of whole blood for *FCGRT*, and GWAS refers to the fructosamine GWAS performed in this study. Left panel reflects correlation of log10 *P* values in the region, and right panel displays the peaks for each phenotype in the region (fructosamine GWAS, top right; *FCGRT* eQTL, bottom right).

ratio (rg = −0.29 [95% CI −0.45 to −0.14]; *P* = 0.0002), waist circumference (rg = −0.32 [−0.50 to −0.14]; *P* = 0.0004), body fat percentage (rg = −0.32 [−0.50 to −0.13]; *P* = 0.0007), and obesity class 1 (rg = −0.29 [−0.45 to −0.12]; *P* = 0.0006).

DISCUSSION

In this study, we aimed to further elucidate the genetic architecture of fructosamine by conducting a GWAS in 20,731 European-ancestry blood donors from the INTERVAL cohort. Combining our data in a meta-analysis with that of 7,647 White individuals previously published by Loomis et al. (7), we identified two loci, *RCN3* and *GCK*, associated with fructosamine levels at genome-wide significance level ($P < 5 \times 10^{-8}$).

GCK (rs3757840) was not previously known to associate with fructosamine levels, but it is a well-established glycemic locus (19); it codes for glucokinase, a key enzyme that plays a role in sensing glucose levels in β-cells (20).

RCN3 (lead variant rs113886122) was shown to associate with fructosamine levels in U.S. White participants by Loomis et al. (7). Variants in this region have previously also been associated with total cholesterol, total protein, albumin, and multiple red cell traits (21,22). In this study, we replicated this association locus in a large sample of European-ancestry blood donors, and, using colocalization analysis with blood eQTL data, we established *FCGRT* as the likely effector transcript in the region. *FCGRT* codes for the Fc fragment of the IgG receptor and transporter, which plays a role in maintenance of albumin levels, protecting albumin from degradation (23). In agreement with these results, the rs59774409-C fructosamine-increasing allele was associated with higher *FCGRT* expression levels in whole blood. In mouse studies, hepatic levels of this protein have been shown to regulate albumin homeostasis and susceptibility to liver injury (24). These results suggest that the locus found in this study could influence fructosamine levels through pathways that regulate albumin levels. As fructosamine normally reflects glycated albumin (1), a shared genetic link is not unexpected.

The *ABCB11* locus previously associated with HbA_{1c} and FG (19) associated with fructosamine at genome-wide significance levels in INTERVAL participants (rs853777, $P = 8.80 \times 10^{-9}$), but failed to reach this threshold after meta-analysis with White participants from Loomis et al. (7) ($P_{meta} = 8.80 \times 10^{-7}$). Given the fact that *ABCB11* is an established glycemic locus (19), testing its association with fructosamine in larger numbers and diverse ancestry participants will be important.

In agreement with a previous study (5), fructosamine appears to be a trait with modest heritability (7.7% [95%

CI −3.6 to 11.9]), suggesting most of the variation of the trait in this generally healthy population is due to environmental factors. This is in keeping with fructosamine measuring short-term changes in glycemia (25) and its use as a measure of treatment response in patients with diabetes (25). In our data, fructosamine does not show evidence of significant genetic correlation with other glycemic traits, including with HbA_{1c} ($P > 0.05$). This is despite both traits normally having a high phenotypic correlation (∼0.61 (26)) and reflecting similar biological processes—namely, the glycation of proteins and having enough power (>80%) to detect a genetic correlation of 0.16. This lack of significant genetic correlation was also observed in Loomis et al. (7).

Interestingly, the only traits for which we observed a Bonferroni significant negative genetic correlation were waist-to-hip ratio, body fat percentage, obesity class 1, and waist circumference. This is consistent with prior studies showing a negative association between BMI and fructosamine (27,28). The effect of adiposity on fructosamine is not fully understood but may impact its use as a clinical measurement of glycemic control.

Lastly, among the genetic correlation results (Supplementary Table 1), nominally significant negative correlations were found with HOMA of β-cell function, platelet count, and estimated glomerular filtration rate, while nominally significant positive genetic correlation was detected with CKD. Given the evidence in the literature linking fructosamine with incident CKD independently of other risk factors in individuals with and without diabetes (2), these correlation results between estimated glomerular filtration rate and CKD provide some interesting hypotheses to explore in future studies.

One limitation of this study is our limited power to detect associations for rarer variants (MAF <1%) due to our sample size (e.g., 28% power to detect an effect size of 0.2-SD units for variants with an MAF of 1%, which is almost double the effect size of the strongest signal in this study).

In conclusion, we have expanded knowledge into the genetic architecture of fructosamine levels by identifying a new genome-wide significant locus (*GCK*), highlighting *FCGRT* as the potential effector transcript at *RCN3*, finding evidence of genetic correlation with obesity-related traits, and replicating the absence of a significant genetic correlation with other glycemic traits in an increased sample size.

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Author Contributions. F.R.M. performed analysis, wrote the paper, and revised, edited, and approved the final version of the paper. J.D. and E.S. contributed data sets and revised, edited, and approved the final version of the paper. D.R., E.D.A., B.Y., N.S., J.D., E.S., and A.S.B. revised, edited, and approved the final version of the paper. I.B. supervised the work, wrote the paper, and revised, edited and approved the final version of the paper. I.B. is the guarantor of this work and, as such, had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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