An expanded genome-wide association study of fructosamine levels identifies *RCN3* as a replicating locus and implicates *FCGRT* as the effector transcript

Fernando Riveros-Mckay[1], David Roberts[2,3,4], Emanuele Di Angelantonio[2,5,6,7], Bing Yu[8], Nicole Soranzo[1,2,9], John Danesh[1,5,8,10], Elizabeth Selvin[11], Adam S Butterworth[2,5,6,8], Inês Barroso[12,1]

[1]Wellcome Sanger Institute, Cambridge, UK, [2]The National Institute for Health Research Blood and Transplant Research Unit (NIHR BTRU) in Donor Health and Genomics, Department of Public Health and Primary Care, University of Cambridge, Cambridge, CB1 8RN, UK., [3]NHS Blood and Transplant - Oxford Centre, Level 2, John Radcliffe Hospital, Headley Way, Oxford OX3 9BQ, UK, [4]Radcliffe Department of Medicine, University of Oxford, John Radcliffe Hospital, Headley Way, Oxford OX3 9DU, UK, [5]British Heart Foundation Cardiovascular Epidemiology Unit, Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK, [6]British Heart Foundation Centre of Research Excellence, University of Cambridge, Cambridge, [7]Health Data Research UK Cambridge, Wellcome Genome Campus and University of Cambridge, Cambridge, UK. [8]Department of Epidemiology, Human Genetics and Environmental Sciences, School of Public Health, University of Texas Health Science Center at Houston,[9]Department of Haematology, University of Cambridge, Cambridge Biomedical Campus, Long Road, Cambridge CB2 0PT, UK ,[10]National Institute for Health Research Cambridge Biomedical Research Centre, University of Cambridge and Cambridge University Hospitals, Cambridge, UK, [11]Department of Epidemiology, Johns Hopkins University, Baltimore, MD, 21202, [12]Exeter Centre of Excellence for Diabetes Research (EXCEED), University of Exeter Medical School, Exeter, UK. Correspondence should be addressed to: Inês Barroso (ines.barroso@exeter.ac.uk).

Abstract (200 words max)

Fructosamine is a measure of short-term glycemic control, which has been suggested as a useful complement to glycated hemoglobin (HbA1c) for the diagnosis and monitoring of diabetes. To date, a single genome-wide association study (GWAS) including 8,951 US White and 2,712 US Black individuals without a diabetes diagnosis has been published. Results in Whites and Blacks yielded different association loci, near *RCN3* and *CNTN5*, respectively. Here we performed a GWAS on 20,731 European ancestry blood donors, and meta-analysed our results with previous data from US White participants from The Atherosclerosis Risk in Communities (ARIC) study (N_{meta}=29,685). We identified a novel association near *GCK* (rs3757840, $beta_{meta}$=0.0062, MAF=0.49, p_{meta}=3.66x10^{-08}) and confirmed the association near *RCN3* (rs113886122, $beta_{meta}$=0.0134, MAF=0.17, p_{meta}= 5.71x10^{-18}). Co-localization analysis with whole blood eQTL 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 HbA1c 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 (HbA1c), which reflects average glycemia during the preceding 3 months, fructosamine measures short-term glycemic control (from 2-3 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 HbA1c to monitor glycemic control in the presence of anemia or a hemoglobinopathy (1). Another important difference is that whereas fructosamine reflects levels of extracellular glucose, HbA1c 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, independently of baseline fasting glucose and HbA1c (1,3), fructosamine has not been widely used as a measure of glucose control (4).

To date, a single study has examined the SNP-based heritability of fructosamine yielding an h^2 estimate of ~13% (5). A fructosamine GWAS performed on 8,951 US White individuals ($N_{discovery}$=7,647) and 2,712 Black individuals ($N_{discovery}$=2,104) without a diabetes diagnosis, found an association in Whites near *RCN3* (rs34459162, $p_{discovery}$=5.3x10^{-9}) and an association near *CNTN5* (rs2438321, $p_{discovery}$=6.2x10^{-9}) in Blacks but neither variant replicated in additional samples ($N_{replication}$=1,304 and $N_{replication}$=608, respectively). This study also demonstrated that, despite some evidence ($p<2.7x10^{-4}$) of association with three established fasting glucose and/or HbA1c loci (*TCF7L2*, *GCK* and *SLC2A2*), there was no significant ($p>0.05$) genetic correlation of fructosamine with fasting glucose or HbA1c.

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 US White participants from the study by Loomis and colleagues (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 non-glycemic 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-analysed our results with those of US White participants from the previously published Atherosclerosis Risk in Communities (ARIC) Study (7). The INTERVAL cohort consists of 47,394 blood donors in the UK (6). The Atherosclerosis Risk in Communities (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 2017 (9). Briefly, samples with poor signal intensity (dish QC<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 multi-allelic variants were excluded. Additionally, before imputation, variants were removed using the following filters: a) HWE p-value<5x10^{-6}; b) call rate<99% over the genotyping batches where the variant did not fail; c) global call rate <75% (over ten 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 (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 lab (http://www.star-shl.nl/) and fructosamine was measured on 28,310 INTERVAL cohort participants using a colorimetric assay (Roche/Hitachi MODULAR P analyser 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 centre, 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 2018 (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. 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 2018 (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 250kb 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<5x10^{-8}). To identify potential effector transcripts at the *RCN3* locus, expression data from GTEx v7 (https://gtexportal.org/) (14) was used to discover co-localized expression QTLs (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 1Mb 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) was 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<5x10^{-8}) loci. The

ABCB11 locus (rs853777, beta=-0.009 (-0.013 – -0.007 95% CI), MAF=0.35, p=8.8x10^{-9}) previously associated with HbA1c and FG (19), and the *RCN3* locus (rs111476047, beta=0.013 (0.009 – 0.017 95% CI), MAF=0.21, p=2.1x10^{-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 dataset with that of White participants from Loomis et al (7). Following meta-analysis (**Table 1, Supplementary Figures 1-4**), two loci were genome-wide significant, *RCN3* (rs113886122, effect allele=C, beta = 0.013 (0.010 – 0.017 95% CI), MAF=0.17, p$_{meta}$=5.71x10^{-18}) and *GCK* (rs3757840, effect allele=T, beta=0.006 (0.004 – 0.008 95% CI), MAF=0.49, p$_{meta}$=3.66x10^{-08}), another established glycemic trait locus (19). In contrast, the association at the *ABCB11* locus was no longer genome-wide significant (p$_{meta}$=8.50x10^{-07}), due to lack of supporting evidence for association at this locus in ARIC (rs853777, effect allele=T, beta= -0.002 (-0.005 – 0.001 95% CI, 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 towards potential effector transcripts at this locus. Of 42 protein-coding genes within 1Mb 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% (3.6%-11.9% 95% CI). Genetic correlation results with anthropometric, glycemic, kidney and blood cell traits (**Supplementary Table 1**) showed evidence of moderate negative genetic correlation (Bonferroni corrected threshold p < 0.0012) with waist-to-hip ratio (rg=-0.29 (-0.45 – -0.14 95% CI), p=0.0002), waist circumference (rg=-0.32 (-0.50 – -0.14 95% CI), p=0.0004) , body fat percentage (rg=-0.32 (-0.50 – -0.13), p=0.0007 and obesity class 1 (rg=-0.29 (-0.45 – -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 and colleagues (7) we identified two loci, *RCN3* and *GCK*, associated with fructosamine levels at genome-wide significance level (p<5x10^{-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 which plays a role in sensing glucose levels in beta cells (20).

RCN3 (lead variant rs113886122) was shown to associate with fructosamine levels in US White participants by Loomis et (7). Variants in this region have previously also been associated with total cholesterol, total protein, albumin and multiple red cell traits(21,22). Here, 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 Fc Fragment of 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 HbA1c and FG (19) associated with fructosamine at genome-wide significance levels in INTERVAL participants (rs853777, p=8.80x10^{-9}), but failed to reach this threshold after meta-analysis with White participants

from Loomis and colleagues (p_{meta}=8.80x10^{-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%-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 diabetes patients (25). In our data, fructosamine does not show evidence of significant genetic correlation with other glycemic traits, including with HbA1c (p>0.05). This, 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 2018 (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, amongst the genetic correlation results (Supplementary Table 1), nominally significant negative correlations were found with HOMA-B, platelet count and eGFR while nominally significant positive genetic correlation was detected with chronic kidney disease (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 eGFR 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 MAF = 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.

Figure Legends

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).

References

1. Danese E, Montagnana M, Nouvenne A, Lippi G. Advantages and pitfalls of fructosamine and glycated albumin in the diagnosis and treatment of diabetes. In: Journal of Diabetes Science and Technology. 2015.

2. Veiga da-Cunha M, Jacquemin P, Delpierre G, Godfraind C, Théate I, Vertommen D, et al. Increased protein glycation in fructosamine 3-kinase-deficient mice. Biochem J [Internet]. 2006 Oct 15;399(2):257–64. Available from: https://pubmed.ncbi.nlm.nih.gov/16819943

3. Selvin E, Rawlings AM, Grams M, Klein R, Sharrett AR, Steffes M, et al. Fructosamine and glycated albumin for risk stratification and prediction of incident diabetes and microvascular complications: A prospective cohort analysis of the Atherosclerosis Risk in Communities (ARIC) study. Lancet Diabetes Endocrinol. 2014;

4. Little RR, Rohlfing CL, Sacks DB. Status of hemoglobin A1c measurement and goals for improvement: From Chaos to order for improving diabetes care. Clinical Chemistry. 2011.

5. Loomis SJ, Tin A, Coresh J, Boerwinkle E, Pankow JS, Köttgen A, et al. Heritability analysis of nontraditional glycemic biomarkers in the Atherosclerosis Risk in Communities Study. Genet Epidemiol. 2019;

6. Moore C, Sambrook J, Walker M, Tolkien Z, Kaptoge S, Allen D, et al. The INTERVAL trial to determine whether intervals between blood donations can be safely and acceptably decreased to optimise blood supply: Study protocol for a randomised controlled trial. Trials. 2014;

7. Loomis SJ, Li M, Maruthur NM, Baldridge AS, North KE, Mei H, et al. Genome-wide association study of serum fructosamine and glycated albumin in adults without diagnosed diabetes: Results from the atherosclerosis risk in communities study. In: Diabetes. 2018.

8. The ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. Am J Epidemiol [Internet]. 1989;129(4):687–702. Available from: http://www.ncbi.nlm.nih.gov/pubmed/2646917

9. Astle WJ, Elding H, Jiang T, Allen D, Ruklisa D, Mann AL, et al. The Allelic Landscape of Human Blood Cell Trait Variation and Links to Common Complex Disease. Cell. 2016;

10. R Development Core Team R. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing. 2011.

11. Loh PR, Tucker G, Bulik-Sullivan BK, Vilhjálmsson BJ, Finucane HK, Salem RM, et al. Efficient Bayesian mixed-model analysis increases association power in large cohorts. Nat Genet. 2015;

12. Willer CJ, Li Y, Abecasis GR. METAL: Fast and efficient meta-analysis of genomewide association scans. Bioinformatics. 2010;

13. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MAR, Bender D, et al. PLINK: A tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet. 2007;

14. Lonsdale J, Thomas J, Salvatore M, Phillips R, Lo E, Shad S, et al. The Genotype-Tissue Expression (GTEx) project. Nature Genetics. 2013.

15. Giambartolomei C, Vukcevic D, Schadt EE, Franke L, Hingorani AD, Wallace C, et al. Bayesian Test for Colocalisation between Pairs of Genetic Association Studies Using Summary Statistics. PLoS Genet. 2014;

16. Bulik-Sullivan B, Loh PR, Finucane HK, Ripke S, Yang J, Patterson N, et al. LD score

regression distinguishes confounding from polygenicity in genome-wide association studies. Nat Genet. 2015;

17. Zheng J, Erzurumluoglu AM, Elsworth BL, Kemp JP, Howe L, Haycock PC, et al. LD Hub: A centralized database and web interface to perform LD score regression that maximizes the potential of summary level GWAS data for SNP heritability and genetic correlation analysis. Bioinformatics. 2017;

18. Visscher PM, Hemani G, Vinkhuyzen AAE, Chen G-B, Lee SH, Wray NR, et al. Statistical power to detect genetic (co)variance of complex traits using SNP data in unrelated samples. PLoS Genet [Internet]. 2014 Apr 10;10(4):e1004269–e1004269. Available from: https://pubmed.ncbi.nlm.nih.gov/24721987

19. Chen J, Spracklen CN, Marenne G, Varshney A, Corbin LJ, Luan J, et al. The trans-ancestral genomic architecture of glycemic traits. Nat Genet [Internet]. 2021;53(6):840–60. Available from: https://doi.org/10.1038/s41588-021-00852-9

20. Matschinsky FM, Wilson DF. The central role of glucokinase in glucose homeostasis: A perspective 50 years after demonstrating the presence of the enzyme in islets of Langerhans. Front Physiol. 2019;

21. Vuckovic D, Bao EL, Akbari P, Lareau CA, Mousas A, Jiang T, et al. The Polygenic and Monogenic Basis of Blood Traits and Diseases. Cell [Internet]. 2020 Sep 3;182(5):1214-1231.e11. Available from: https://pubmed.ncbi.nlm.nih.gov/32888494

22. Kanai M, Akiyama M, Takahashi A, Matoba N, Momozawa Y, Ikeda M, et al. Genetic analysis of quantitative traits in the Japanese population links cell types to complex human diseases. Nat Genet [Internet]. 2018;50(3):390–400. Available from: http://europepmc.org/abstract/MED/29403010

23. Chaudhury C, Mehnaz S, Robinson JM, Hayton WL, Pearl DK, Roopenian DC, et al. The major histocompatibility complex-related Fc receptor for IgG (FcRn) binds albumin and prolongs its lifespan. J Exp Med. 2003;

24. Pyzik M, Rath T, Kuo TT, Win S, Baker K, Hubbard JJ, et al. Hepatic FcRn regulates albumin homeostasis and susceptibility to liver injury. Proc Natl Acad Sci U S A. 2017;

25. Lee J-E. Alternative biomarkers for assessing glycemic control in diabetes: fructosamine, glycated albumin, and 1,5-anhydroglucitol. Ann Pediatr Endocrinol Metab. 2015;

26. Zafon C, Ciudin A, Valladares S, Mesa J, Simó R. Variables Involved in the Discordance between HbA1c and Fructosamine: The Glycation Gap Revisited. PLoS One. 2013;

27. Nouya AY, Nansseu JRN, Moor VJA, Pieme CA, Noubiap JJN, Tchoula CM, et al. Determinants of fructosamine levels in a multi-ethnic Sub-Saharan African population. Diabetes Res Clin Pract. 2015;

28. Broussolle C, Tricot F, Garcia I, Orgiazzi J, Revol A. Evaluation of the fructosamine test in obesity: consequences for the assessment of past glycemic control in diabetes. Clin Biochem. 1991;

29. Liu B, Gloudemans MJ, Rao AS, Ingelsson E, Montgomery SB. Abundant associations with gene expression complicate GWAS follow-up. Nature Genetics. 2019.

SNP	Chr	MAF	Position	A1	A2	INTERVAL			ARIC			Meta-Analysis			Nearest Gene
						beta	SE	p-val	Beta	SE	p-val	beta	SE	p-value	
rs113886122	19	0.17	50044741	c	g	0.0139	0.0021	4.90×10^{-11}	0.0129	0.0023	1.70×10^{-08}	0.0134	0.0016	5.71×10^{-18}	*RCN3* (intron)
rs853777	2	0.35	169812217	c	t	-0.0099	0.0017	8.80×10^{-09}	-0.0022	0.0016	1.70×10^{-01}	-0.0058	0.0012	8.50×10^{-07}	*ABCB11* (intron)
rs3757840	7	0.49	44231216	t	g	0.0049	0.0016	1.80×10^{-03}	0.0075	0.0016	2.80×10^{-06}	0.0062	0.0011	3.66×10^{-08}	*GCK* (upstream)

Table 1: Genome-wide significant loci in INTERVAL GWAS and/or meta-analysis. MAF= Minor allele frequency in INTERVAL. POS= Position in hg19. A1 = Trait increasing allele. A2 = Other allele. META PVAL= Meta-analysis p-value.). Betas are presented as log values of fructosamine in µmol/L units

1
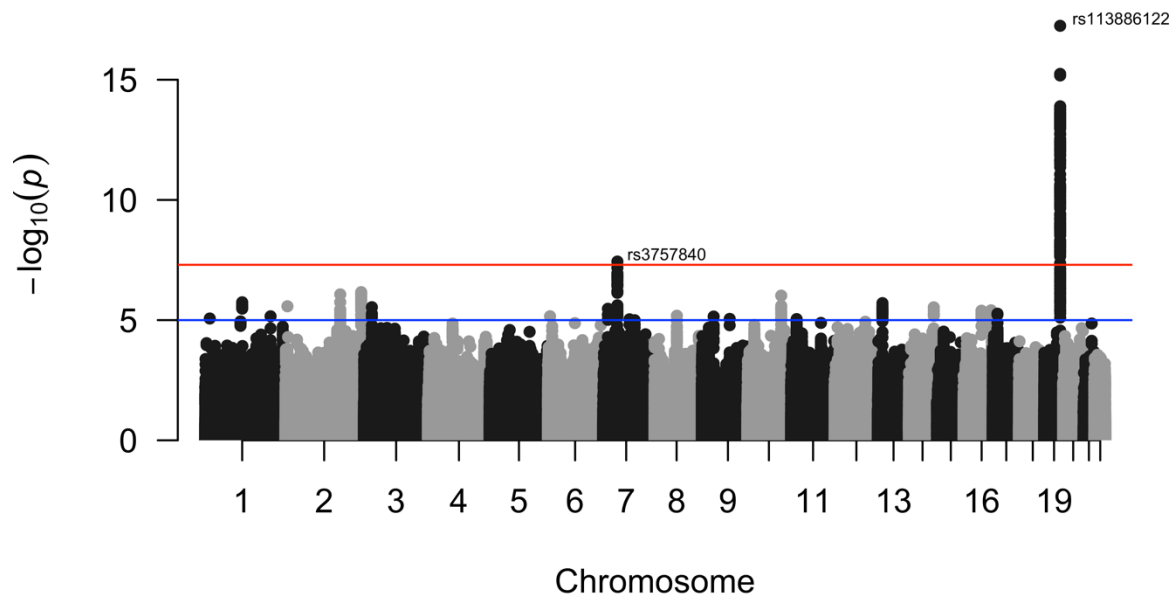
Supplementary Figure 1: Manhattan plot of fructosamine meta-analysis. Blue horizontal line represents a p-value of 1×10^{-5}. Red line represents genome-wide significant threshold (5×10^{-8}). Lead SNPs of genome-wide significant loci highlighted.
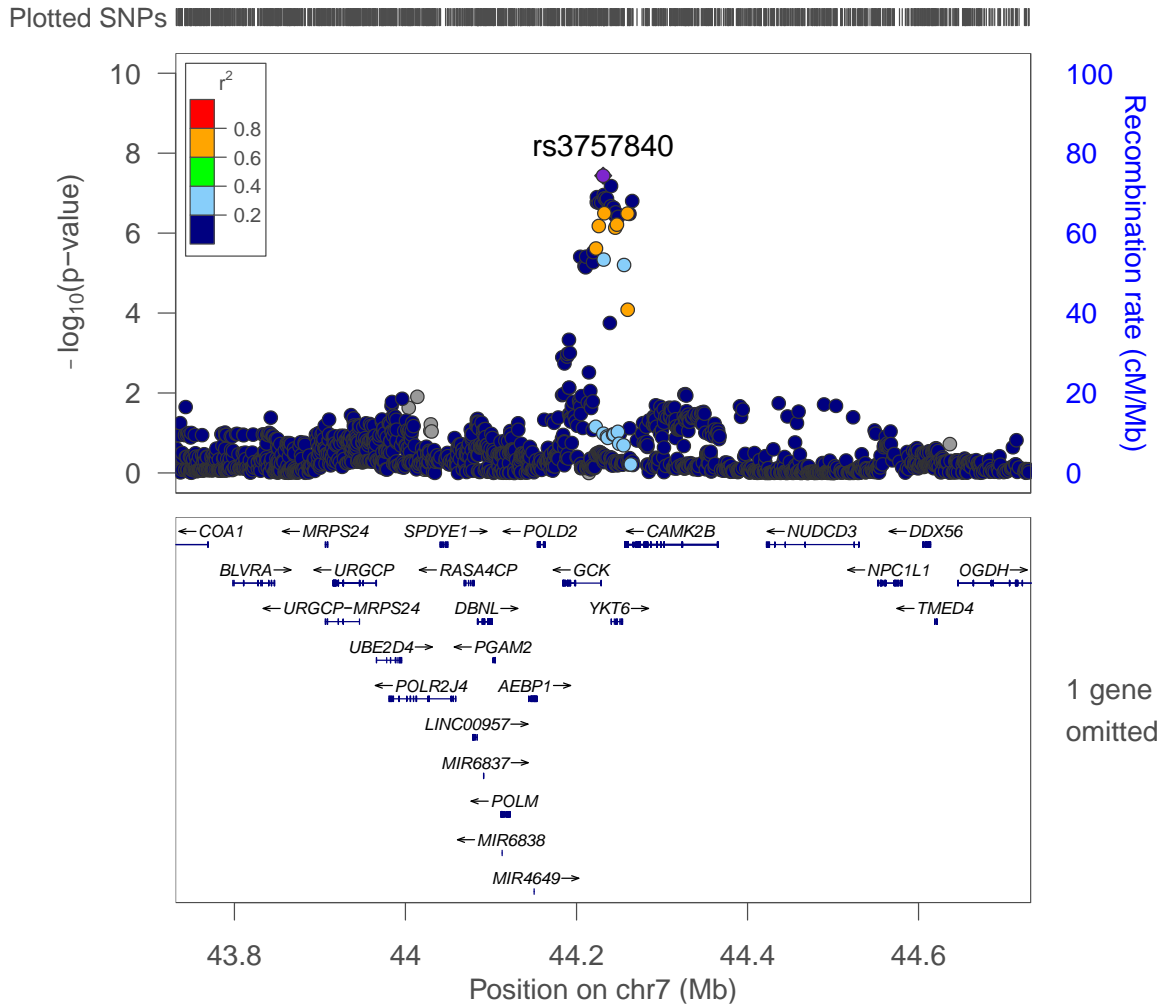
Supplementary Figure 2: Locus zoom plot for GCK locus.
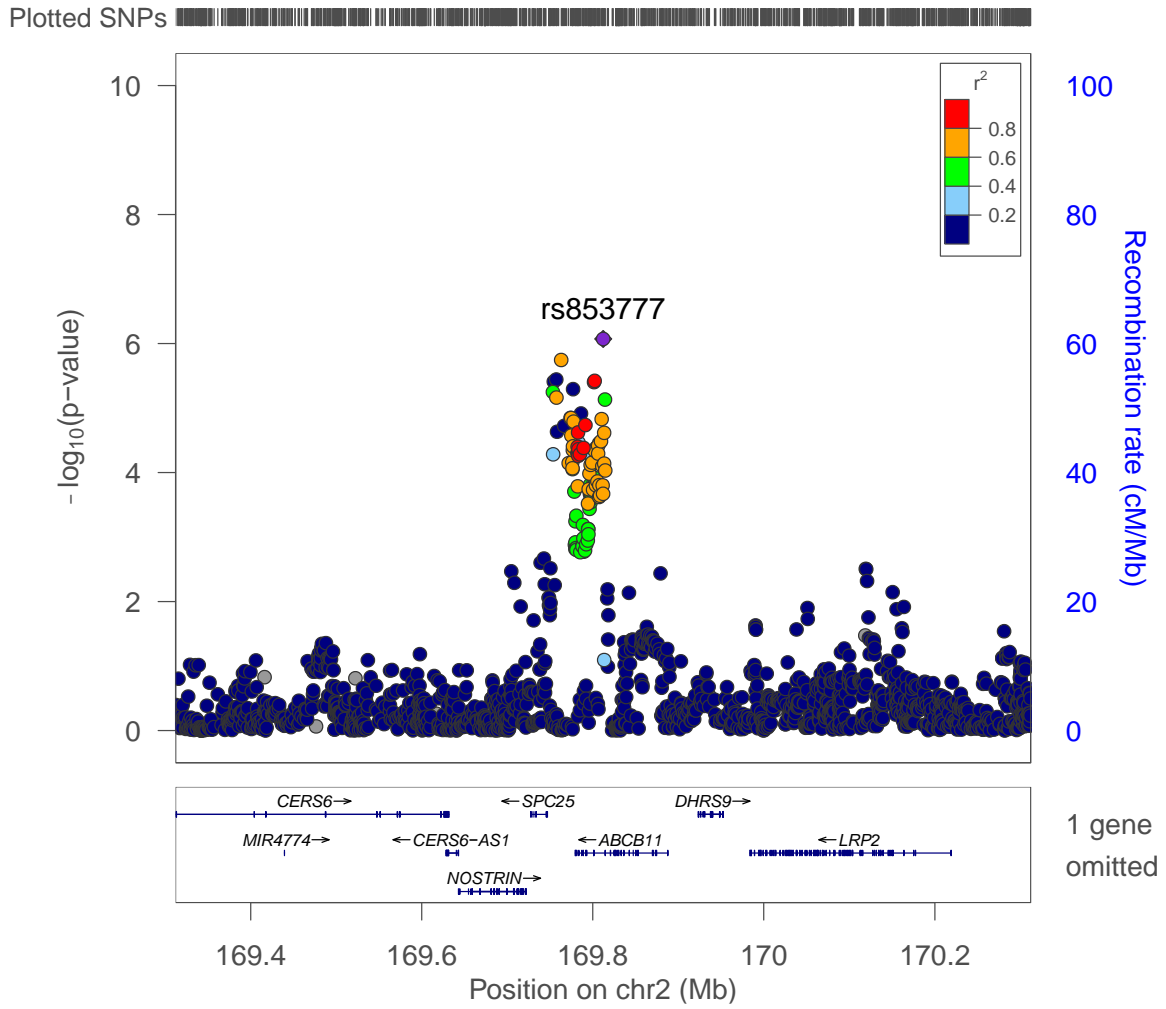
Supplementary Figure 3: Locus zoom plot for ABCB11 locus.
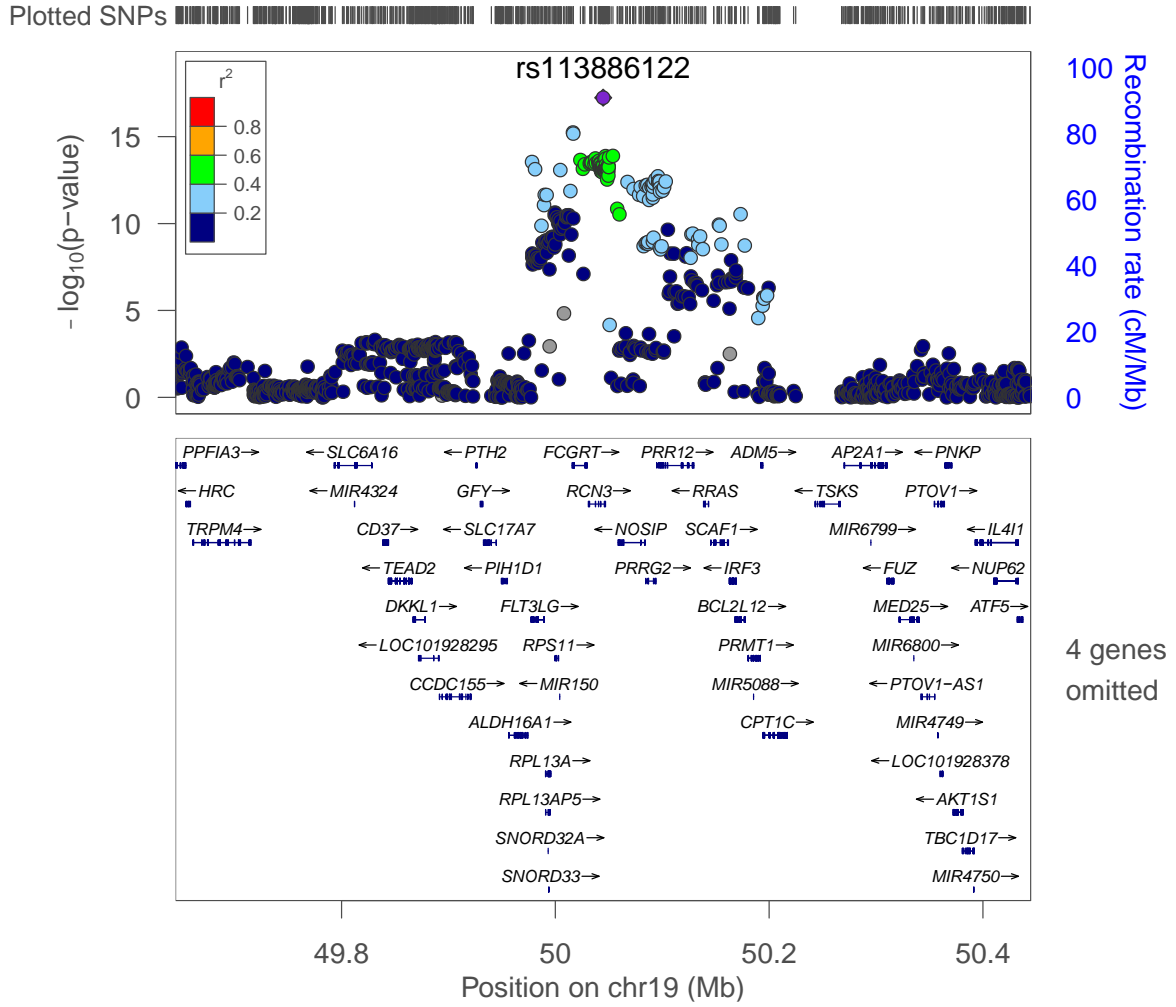
Supplementary Figure 4: Locus zoom plot for RCN3 locus.
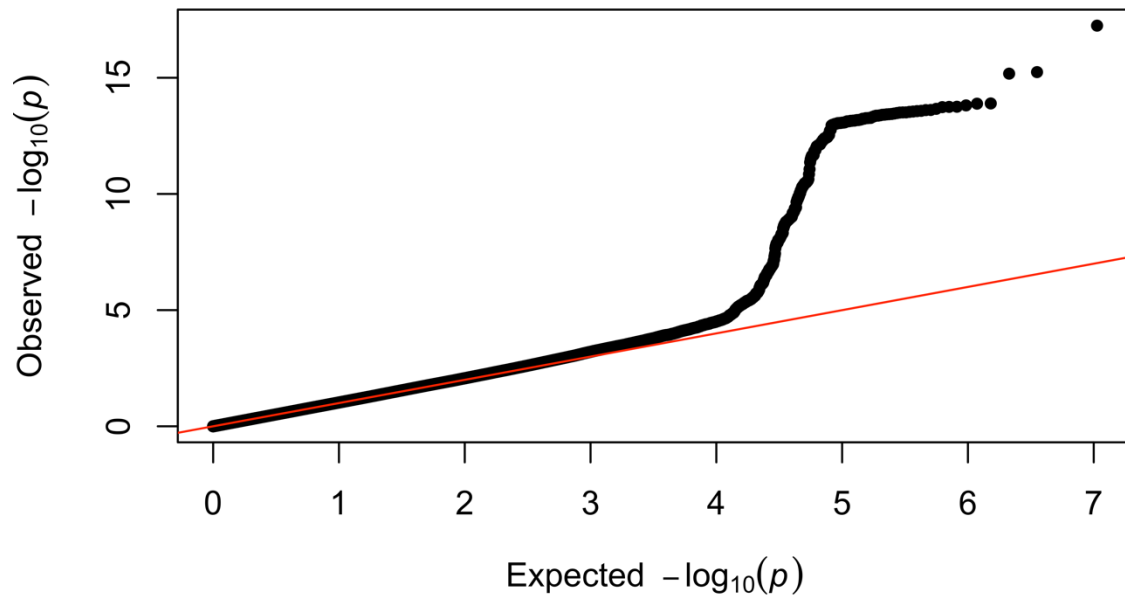
Supplementary Figure 5: QQ plot for fructosamine meta-analysis.

Trait	PMID	Category	ethnicity	rg	se	z	p
Waist-to-hip ratio	25673412	anthropometric	European	-0.2943	0.0794	-3.7074	0.0002
Waist circumference	25673412	anthropometric	European	-0.3197	0.0898	-3.5603	0.0004
Obesity class 1	23563607	anthropometric	European	-0.285	0.0828	-3.4441	0.0006
Body fat	26833246	anthropometric	Mixed	-0.3174	0.0942	-3.3708	0.0007
Obesity class 2	23563607	anthropometric	European	-0.2747	0.0965	-2.8458	0.0044
Body mass index	20935630	anthropometric	European	-0.2458	0.0871	-2.8226	0.0048
HOMA-B	20081858	glycemic	European	-0.4426	0.1673	-2.645	0.0082
Overweight	23563607	anthropometric	European	-0.2267	0.088	-2.5755	0.01
eGFR based on serum creatinine	26831199	kidney	Mixed	-0.2351	0.094	-2.5026	0.0123
eGFR based on serum creatinine (non-diabetes)	26831199	kidney	Mixed	-0.2264	0.0976	-2.32	0.0203
Platelet count	22139419	haemotological	European	-0.2329	0.1034	-2.2518	0.0243
Chronic Kidney Disease	26831199	kidney	Mixed	0.399	0.1927	2.07	0.0385
Hip circumference	25673412	anthropometric	European	-0.1838	0.0927	-1.9825	0.0474
Obesity class 3	23563607	anthropometric	European	-0.2428	0.126	-1.9272	0.054
Extreme bmi	23563607	anthropometric	European	-0.2067	0.1099	-1.8818	0.0599
Fasting glucose main effect	22581228	glycemic	European	0.2457	0.1323	1.8565	0.0634
Extreme height	23563607	anthropometric	European	0.1432	0.0859	1.6657	0.0958
Infant head circumference	22504419	anthropometric	European	0.2753	0.1699	1.6203	0.1052
Fasting insulin main effect	22581228	glycemic	European	-0.2377	0.1548	-1.536	0.1245

Sitting height ratio	25865494	anthropometric	European	0.1896	0.1405	1.3495	0.1772
2hr glucose adjusted for BMI	20081857	glycemic	European	-0.2933	0.2201	-1.3328	0.1826
Fasting proinsulin	20081858	glycemic	European	-0.2306	0.1765	-1.3069	0.1913
Height_2010	20881960	anthropometric	European	0.0895	0.0685	1.3058	0.1916
Child birth length	25281659	anthropometric	European	0.204	0.1565	1.3041	0.1922
Extreme waist-to-hip ratio	23563607	anthropometric	European	-0.2041	0.1591	-1.2826	0.1996
Type 2 Diabetes	22885922	glycemic	European	0.1446	0.1291	1.1204	0.2625
HOMA-IR	20081858	glycemic	European	-0.2166	0.1995	-1.0856	0.2776
Heart rate	23583979	haemotological	Mixed	-0.1026	0.1128	-0.9098	0.3629
Birth weight	27680694	anthropometric	European	0.0639	0.0869	0.7347	0.4625
HbA1C	20858683	glycemic	European	0.0939	0.1613	0.5825	0.5602
Serum cystatin c	26831199	kidney	Mixed	0.05	0.1144	0.437	0.6621
Height; Females at age 10 and males at age 12	23449627	anthropometric	European	0.0397	0.1234	0.322	0.7474
Child birth weight	23202124	anthropometric	European	0.0455	0.1489	0.3053	0.7601
Difference in height between childhood and adulthood; age 8	23449627	anthropometric	European	0.0345	0.1437	0.2403	0.8101
Urinary albumin-to-creatinine ratio (non-diabetes)	26631737	kidney	European	-0.0248	0.1714	-0.1447	0.8849
Mean platelet volume	22139419	haemotological	European	0.0154	0.1078	0.1426	0.8866
Urinary albumin-to-creatinine ratio	26631737	kidney	European	0.0211	0.1592	0.1325	0.8946
Difference in height between adolescence and adulthood; age 14	23449627	anthropometric	European	0.0153	0.1711	0.0896	0.9286
Childhood obesity	22484627	anthropometric	European	-0.0047	0.1172	-0.04	0.9681

Supplementary Table 1: Genetic correlation results for fructosamine meta-analysis.
rg=genetic correlation estimate. se=standard error of estimate. z=z score. p=p-value.

eQTL	Posterior probabilty
SNRNP70	0.02091
LIN7B	0.010718017
C19orf73	0.014784497
PPFIA3	0.013961669
HRC	0.015488361
TRPM4	0.000623167
SLC6A16	6.69E-05
CD37	8.91E-06
TEAD2	0.000385792
SLC17A7	0.018770708
PIH1D1	0.020056163
ALDH16A1	1.06E-12
FLT3LG	0.021009203
RPL13A	0.014670253
RPS11	0.009310853
hsa-mir-150	0.01548654
FCGRT	0.977157882

RCN3	0.629436415
NOSIP	0.016954363
PRRG2	0.013823592
PRR12	0.114863225
RRAS	0.022434557
SCAF1	0.021890013
IRF3	0.022896502
BCL2L12	0.017701827
PRMT1	0.015474111
ADM5	0.014415826
CPT1C	0.575995001
TSKS	0.000108332
AP2A1	0.02184052
FUZ	0.020351908
MED25	0.016222586
PTOV1	0.000157996
PNKP	5.18E-13
AKT1S1	0.01395365
TBC1D17	0.014229038
IL4I1	0.010720632
NUP62	0.012523085
ATF5	0.025055285
SIGLEC11	4.43E-13
VRK3	0.012189455
ZNF473	0.000175039

Supplementary Table 2: Coloc results for RCN3 locus.

Trait	PMID	Category	ethnicity	rg	se	z	p
Waist-to-hip ratio	25673412	anthropomet	European	-0.2943	0.0794	-3.7074	0.0002
Waist circumference	25673412	anthropomet	European	-0.3197	0.0898	-3.5603	0.0004
Obesity class 1	23563607	anthropomet	European	-0.285	0.0828	-3.4441	0.0006
Body fat	26833246	anthropomet	Mixed	-0.3174	0.0942	-3.3708	0.0007
Obesity class 2	23563607	anthropomet	European	-0.2747	0.0965	-2.8458	0.0044
Body mass index	20935630	anthropomet	European	-0.2458	0.0871	-2.8226	0.0048
HOMA-B	20081858	glycemic	European	-0.4426	0.1673	-2.645	0.0082
Overweight	23563607	anthropomet	European	-0.2267	0.088	-2.5755	0.01
eGFR based on serum creatinine	26831199	kidney	Mixed	-0.2351	0.094	-2.5026	0.0123
eGFR based on serum creatinine (n	26831199	kidney	Mixed	-0.2264	0.0976	-2.32	0.0203
Platelet count	22139419	haemotologic	European	-0.2329	0.1034	-2.2518	0.0243
Chronic Kidney Disease	26831199	kidney	Mixed	0.399	0.1927	2.07	0.0385
Hip circumference	25673412	anthropomet	European	-0.1838	0.0927	-1.9825	0.0474
Obesity class 3	23563607	anthropomet	European	-0.2428	0.126	-1.9272	0.054
Extreme bmi	23563607	anthropomet	European	-0.2067	0.1099	-1.8818	0.0599
Fasting glucose main effect	22581228	glycemic	European	0.2457	0.1323	1.8565	0.0634
Extreme height	23563607	anthropomet	European	0.1432	0.0859	1.6657	0.0958
Infant head circumference	22504419	anthropomet	European	0.2753	0.1699	1.6203	0.1052
Fasting insulin main effect	22581228	glycemic	European	-0.2377	0.1548	-1.536	0.1245
Sitting height ratio	25865494	anthropomet	European	0.1896	0.1405	1.3495	0.1772
2hr glucose adjusted for BMI	20081857	glycemic	European	-0.2933	0.2201	-1.3328	0.1826
Fasting proinsulin	20081858	glycemic	European	-0.2306	0.1765	-1.3069	0.1913
Height_2010	20881960	anthropomet	European	0.0895	0.0685	1.3058	0.1916
Child birth length	25281659	anthropomet	European	0.204	0.1565	1.3041	0.1922
Extreme waist-to-hip ratio	23563607	anthropomet	European	-0.2041	0.1591	-1.2826	0.1996
Type 2 Diabetes	22885922	glycemic	European	0.1446	0.1291	1.1204	0.2625
HOMA-IR	20081858	glycemic	European	-0.2166	0.1995	-1.0856	0.2776
Heart rate	23583979	haemotologic	Mixed	-0.1026	0.1128	-0.9098	0.3629
Birth weight	27680694	anthropomet	European	0.0639	0.0869	0.7347	0.4625
HbA1C	20858683	glycemic	European	0.0939	0.1613	0.5825	0.5602

Serum cystatin c	26831199	kidney	Mixed	0.05	0.1144	0.437	0.6621
Height; Females at age 10 and male	23449627	anthropomet	European	0.0397	0.1234	0.322	0.7474
Child birth weight	23202124	anthropomet	European	0.0455	0.1489	0.3053	0.7601
Difference in height between childh	23449627	anthropomet	European	0.0345	0.1437	0.2403	0.8101
Urinary albumin-to-creatinine ratio	26631737	kidney	European	-0.0248	0.1714	-0.1447	0.8849
Mean platelet volume	22139419	haemotologic	European	0.0154	0.1078	0.1426	0.8866
Urinary albumin-to-creatinine ratio	26631737	kidney	European	0.0211	0.1592	0.1325	0.8946
Difference in height between adole	23449627	anthropomet	European	0.0153	0.1711	0.0896	0.9286
Childhood obesity	22484627	anthropomet	European	-0.0047	0.1172	-0.04	0.9681

eQTL	Posterior probabilty
SNRNP70	0.02091
LIN7B	0.010718017
C19orf73	0.014784497
PPFIA3	0.013961669
HRC	0.015488361
TRPM4	0.000623167
SLC6A16	6.69E-05
CD37	8.91E-06
TEAD2	0.000385792
SLC17A7	0.018770708
PIH1D1	0.020056163
ALDH16A1	1.06E-12
FLT3LG	0.021009203
RPL13A	0.014670253
RPS11	0.009310853
hsa-mir-150	0.01548654
FCGRT	0.977157882
RCN3	0.629436415
NOSIP	0.016954363
PRRG2	0.013823592
PRR12	0.114863225
RRAS	0.022434557
SCAF1	0.021890013
IRF3	0.022896502
BCL2L12	0.017701827
PRMT1	0.015474111
ADM5	0.014415826
CPT1C	0.575995001
TSKS	0.000108332
AP2A1	0.02184052
FUZ	0.020351908
MED25	0.016222586
PTOV1	0.000157996
PNKP	5.18E-13
AKT1S1	0.01395365
TBC1D17	0.014229038
IL4I1	0.010720632
NUP62	0.012523085
ATF5	0.025055285
SIGLEC11	4.43E-13
VRK3	0.012189455
ZNF473	0.000175039