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ORIGINAL RESEARCH

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Genome-wide association study identifying novel variant for fasting insulin and allelic heterogeneity in known glycemic loci in Chilean adolescents: The Santiago Longitudinal Study

Victoria L Buchanan[1] | Yujie Wang[1] | Estela Blanco[2] | Mariaelisa Graff[1] | Cecilia Albala[3] | Raquel Burrows[3] | José L Santos[4] | Bárbara Angel[3] | Betsy Lozoff[5] | Venkata Saroja Voruganti[6] | Xiuqing Guo[7] | Kent D Taylor[7] | Yii-Der Ida Chen[7] | Jie Yao[7] | Jingyi Tan[7] | Carolina Downie[1] | Heather M Highland[1] | Anne E Justice[1,8] | Sheila Gahagan[2] | Kari E North[1]

[1]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina

[2]Division of Academic General Pediatrics, Child Development and Community Health, University of California at San Diego, San Diego, California

[3]Department of Public Health Nutrition, Institute of Nutrition and Food Technology, University of Chile, Santiago, Chile

[4]Department of Nutrition, Diabetes and Metabolism, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile

[5]Department of Pediatrics, University of Michigan, Ann Arbor, Michigan

[6]Department of Nutrition and UNC Nutrition Research Institute, University of North Carolina at Chapel Hill, Kannapolis, North Carolina

[7]The Institute for Translational Genomics and Population Sciences, Department of Pediatrics, The Lundquist Institute at Harbor-UCLA Medical Center, Torrance, California

[8]Department of Population Health Sciences, Geisinger, Danville, Pennsylvania

Correspondence
Victoria L Buchanan, Department of Epidemiology, University of North Carolina at Chapel Hill, 123 W. Franklin Street, Building C, Suite 4217, Chapel Hill, NC 27599, USA.
Email: vicbucha@live.unc.edu

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Summary

Background: The genetic underpinnings of glycemic traits have been understudied in adolescent and Hispanic/Latino (H/L) populations in comparison to adults and populations of European ancestry.

Objective: To identify genetic factors underlying glycemic traits in an adolescent H/L population.

Methods: We conducted a genome-wide association study (GWAS) of fasting glucose (FG) and fasting insulin (FI) in H/L adolescents from the Santiago Longitudinal Study.

Results: We identified one novel variant positioned in the *CSMD1* gene on chromosome 8 (rs77465890, effect allele frequency = 0.10) that was associated with FI (β = –0.299, SE = 0.054, $p = 2.72\times10^{-8}$) and was only slightly attenuated after adjusting for body mass index z-scores (β = –0.252, SE = 0.047, $p = 1.03\times10^{-7}$). We demonstrated directionally consistent, but not statistically significant results in African and Hispanic adults of the Population Architecture Using Genomics and Epidemiology Consortium. We also identified secondary signals for two FG loci after conditioning on known variants, which demonstrate allelic heterogeneity in well-known glucose loci.

Abbreviations: AMR, admixed American reference panel; ARIC, Atherosclerosis Risk in Communities Study; BMIz, body mass index z-scores; BP, base pair position (hg19 build); CARDIA, Coronary Artery Risk Development in Young Adults Study; CHR, chromosome; EA/OA, effect allele/ other allele; EAF, effect allele frequency; FG, fasting glucose; FI, fasting insulin; GWAS, genome-wide association study; H/L, Hispanic/Latino; HCHS/SOL, Hispanic Community Health Study/ Study of Latinos; HOMA-IR, homeostatic model assessment of insulin resistance; LD, linkage disequilibrium; MAGIC, Meta-Analysis of Glucose and Insulin-related Traits Consortium; MEC, Multiethnic Cohort Study; MEGA, Multiethnic Genotyping Array; NASH, Nonalcoholic Steatohepatitis Study; PAGE, Population Architecture using Genomics and Epidemiology Consortium; PCs, principal components; QC, quality control; SE, standard error; SLS, Santiago Longitudinal Study; SNP, single nucleotide polymorphism; T2D, type 2 diabetes; WHI, Women's Health Initiative.

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Conclusion: Our results exemplify the importance of including populations with diverse ancestral origin and adolescent participants in GWAS of glycemic traits to uncover novel risk loci and expand our understanding of disease aetiology.

KEYWORDS
adolescent, glucose, GWAS, insulin

1 | INTRODUCTION

The prevalence of type 2 diabetes (T2D) among adults has been rising globally,[1,2] especially among low- and middle-income countries,[2] and is projected to increase from an estimated 8.8% in 2015 to over 10% by 2040.[3] Alarmingly, T2D is increasingly common among adolescents and young adults, particularly in Hispanic/Latinos (H/L).[4] Diet and physical activity changes from urbanization and rapid socioeconomic improvement in Chile have resulted in ~75% of its population over age 15 being overweight or obese[5] and a prevalence of T2D among the highest in South America.[3]

Insulin resistance and elevated blood glucose often precede T2D and increase the risk of developing T2D over time.[6,7] In addition to well-established factors like obesity, poor diet, and physical inactivity, genetic factors also contribute to variation in glycemic traits and T2D risk.[8,9] Genetic underpinnings of these traits, however, have been understudied in adolescents and H/L populations, despite shouldering an increasing burden of obesity and T2D.

Studying populations at distinct periods across the life-course, that are ancestrally diverse, and that have heightened disparities of disease risk is important for several reasons. First, the literature for complex traits, including for T2D-related traits like insulin resistance, suggests that there may be distinct genetic effects present during adolescence.[10-13] Second, it allows for identification of variants unique to genetically admixed populations, which may be absent or rare in other populations. Third, generalizing previously identified associations in a different population provides stronger evidence that the genetic effect is relevant across multiple populations and gene-environment contexts.

We therefore conducted a genome-wide association study (GWAS) of glycemic traits—fasting glucose (FG) and fasting insulin (FI)—measured during adolescence in Chileans of the Santiago Longitudinal Study (SLS). Our aims were to (1) determine if novel large effects were segregating in this population and (2) describe the association of known loci for these traits in a diverse H/L population.

2 | METHODS

2.1 | Study population

The SLS is a cohort of participants from Santiago, Chile followed from infancy to adulthood. The parent study—details of which are described elsewhere—recruited 1798 infants from 1991 to 1996 born at term, weighing at least 3.0 kg, and with no major health issues, to participate in a randomized trial of iron supplementation to prevent iron deficiency anaemia.[14] Families of participants were literate and low- to middle-income.[14,15] Participants were followed during infancy and at ages 5, 10, 16 or 17, and 21 or 22 years and assessed for a variety of outcomes.[16,17] Parents provided informed consent for all visits occurring during childhood; participants also provided assent at the age 10 and adolescent visits and informed consent at 21 or 22 years. A total of 679 of the original participants were included in an ancillary cardiovascular health study during the adolescent visits, which included traits of interest described below. This number decreased after excluding individuals for whom we did not have genetic data, genetic data did not pass quality control (QC) measures or the traits were unavailable for these individuals. This study has been approved by Institutional Review Boards at the University of California at San Diego, University of Michigan, University of North Carolina at Chapel Hill, and the Institute of Nutrition and Food Technology, University of Chile.

2.2 | Trait measurements

2.2.1 | Glycemic traits

After fasting overnight for 8–12 h before the adolescent visits occurring at age 16–17, participants' blood was drawn to assess FG and FI levels. Glucose was measured with an enzymatic colorimetric assay (QCA S.A., Amposta, Spain), and insulin was measured with radioimmunoassay (RIA DCP Diagnostic Products Corporation, LA, USA). We additionally considered estimates of homeostatic model assessment of insulin resistance (HOMA-IR) using the following formula[18]:

$$\frac{\text{fasting insulin}\left(\frac{\mu IU}{ml}\right) \times \text{fasting glucose}\left(\frac{mmol}{l}\right)}{22.5}.$$

2.2.2 | Anthropometric traits

A study nurse or physician used standard techniques to measure height to the nearest 0.1 cm with a Holtain stadiometer and weight to

the nearest 0.1 kg with a SECA scale. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2), then transformed into z-scores (BMIz) relative to Centers for Disease Control anthropometric reference data (2007–2010).[19]

2.3 | Genotyping and identifying known loci

DNA was extracted from participants' blood, genotyped using the Illumina Multiethnic Genotyping Array (MEGA) which includes a GWAS scaffold designed to tag both common and low frequency variants in global populations, and imputed using the 1000 Genomes Phase III admixed American reference panel (AMR). QC exclusions included individual call rate > 90%, single nucleotide polymorphism (SNP) call rate > 95%, imputation quality <0.5, minor allele count >10, gender mismatch, and ancestry outliers. To assess novelty and generalization of SNP-phenotype effects, we identified previously reported SNP associations with FG, FI and HOMA-IR at the conventionally accepted GWAS level of significance ($p < 5\times10^{-8}$) in adults and/or children from publications listed in the NHGRI-EBI GWAS Catalog,[20] as of June 19, 2018, as well as from the literature; this included 78 known FG variants in 43 loci, 32 known FI variants in 22 loci, and 9 known HOMA-IR variants in 9 loci.[21-24]

2.4 | Statistical analysis

2.4.1 | Genome-wide association study

Glycemic traits of interest (FG, FI, and HOMA-IR) displayed a non-normal distribution. Therefore, FI and HOMA-IR were natural log-transformed, and one FG outlier was Winsorized to the next lowest value (assessed using SAS v9.4).[25] For genetic association testing, we conducted linear regression of each of the three traits assuming an additive genetic model and adjusting for sex and population substructure using the first five principal components (PCs) calculated in EIGENSTRAT[26] with genome-wide data. Sensitivity analyses also adjusted for BMIz. All participants were essentially the same age [mean 16.8 years (SD = 0.3)]. Age was initially considered for inclusion but did not appear to have a meaningful effect and was dropped from the regression models. Association analyses were conducted using SUGEN,[27] with clumping into independent loci using the EasyStrata R package.[28]

2.4.2 | Interrogation of known associations

We also examined how previously reported SNP-trait associations for glycemic traits generalized to our cohort. As these associations are already established, we considered generalizations of known loci when effect estimates were directionally consistent and nominally significant ($p < 0.05$).

2.4.3 | Conditional analysis

To identify secondary signals in known loci, we evaluated any SNP-trait associations that displayed suggestive significance ($p < 5 \times 10^{-6}$) and were positioned within the 1 Mb region (+/−500 kb) of a previously reported SNP. Signals were considered to be attenuated if the *p*-value decreased below the suggestive level of significance or the beta decreased by more than 10%. Significance of secondary signals was defined using Bonferroni correction for the number of independent SNPs in each 1 Mb interval of the evaluated loci (linkage disequilibrium [LD]-pruned at $r^2 < 0.10$) and provide evidence of allelic heterogeneity at known loci.

2.4.4 | Validation analyses

To validate novel associations reaching suggestive or genome-wide significance in SLS participants, we interrogated SNP-trait associations in several published and unpublished study populations. First, we downloaded summary statistics from the 2010 study entitled "New genetic loci implicated in fasting glucose homeostasis and their impact on T2D risk," published in Nature Genetics 42 (2): 105-16 for our FI and HOMA-IR variants.[29] The studies participating in Meta-Analyses of Glucose and Insulin-Related Traits Consortium (MAGIC) contributed a total of 38 238 individuals for FI and 37 037 for HOMA-IR, from up to 17 population-based cohort studies and four case-control studies and 28 population-based and five case-control studies in the MAGIC discovery and replication stages, respectively. Exclusion criteria included pregnancy, non-fasting individuals, type 1 diabetes and outliers ±3 SD of distribution for either FG or FI. FG was measured from fasting whole blood, plasma, serum or a combination of these. HOMA-IR was derived from paired fasting glucose and insulin measures. Commercial genome-wide arrays were used for genotyping individual studies. Additional autosomal SNPs were imputed from the HapMap CEU (European ancestry) reference panel using MACH,[30] IMPUTE[31] or BIMBAM[32] software.

Second, we looked up results in the Nonalcoholic Steatohepatitis (NASH) Clinical Research Network (CRN) in the Nonalcoholic Fatty Liver Disease (NAFLD) Database Study.[33] Participants in this prospective, longitudinal cohort were self-identified Hispanic adolescent males with liver biopsies that met exclusion criteria ruling out other contributors to NAFLD ($n = 234$). Only males were included in order to limit heterogeneity in the sample.

Lastly, we assessed the evidence for association in our multi-ethnic cohort, the Population Architecture using Genomics and Epidemiology (PAGE) Consortium. PAGE participants without diabetes from the Atherosclerosis Risk in Communities (ARIC) Study, the Coronary Artery Risk Development in Young Adults (CARDIA) Study, the Multiethnic Cohort (MEC) Study, the Hispanic Community Health Study/Study of Latinos and the Women's Health Initiative (WHI) were included in the FI analysis. The PAGE populations were genotyped in two ways: 21 430 participants with FI measurements were genotyped using the MEGA array, and another 26 965 participants with FI measurements from ARIC, CARDIA, MEC and WHI were previously genotyped using either

TABLE 1 Characteristics of Santiago Longitudinal Study participants (n = 543) at adolescent assessments

Characteristic	n (%) or mean (SD)
Female	259 (47.7)
Age (years)	16.8 (0.3)
Body mass index (BMI) (kg/m^2)	23.8 (4.6)
BMI Z-scores	0.53 (0.99)
Fasting glucose (mg/dl)	88.44 (9.78)
Fasting insulin (μUI/dl)	8.11 (5.57)
HOMA-IR (glucose × insulin/405)	1.80 (1.34)

Note: No participants were considered diabetic or on treatment for diabetes at this time.

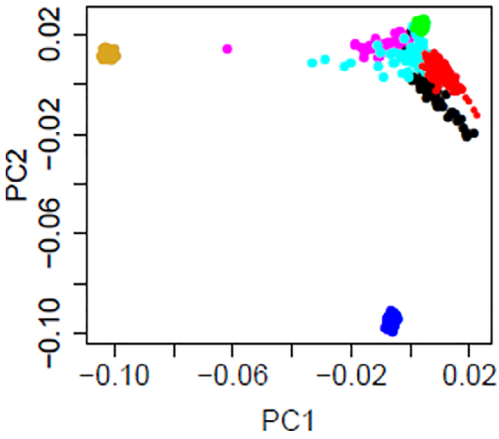

FIGURE 1 Principal components of ancestry for study sample of Santiago Longitudinal Study (SLS) participants plotted with reference populations from the 1000 Genomes project. (Chile: SLS participants; CEU: Utah residents with Northern and Western European ancestry; CHB: Han Chinese in Beijing, China; YRI: Yoruba in Ibadan, Nigeria; CLM: Colombians from Medellin, Colombia; MXL: Mexican ancestry from Los Angeles, USA; PUR: Puerto Ricans)

Illumina or Affymetrix arrays within each individual study and imputed to the 1000 Genome Phase 3 panel. Variants with an effective N within study greater than 30 were tested for association with Blom-transformed natural-log transformed FI, adjusted for age, sex, age-sex interaction, self-reported race/ethnicity, study center, the top 10 PCs for genetic ancestry, and BMI (in secondary analyses). Association analyses for each study were performed using SUGEN.[27] Subsequently, fixed-effects models with inverse variance weighting were used to pool study-specific SNP effect estimates and their SEs by race/ethnicity, using METAL.[34] After QC, data were available for validation analysis of rs77465890 for 44 280 PAGE participants, most of whom were of European (n = 18 637), Hispanic (n = 14 270), or African (n = 7683) ancestry and imputation information >0.8.

3 | RESULTS

3.1 | Descriptive statistics

After phenotypic and genotypic QC assessment, data were available for 543 SLS individuals (47.7% female) participating in the adolescent cardiometabolic exam. Descriptive statistics are shown in Table 1. Importantly, given the young age of our study participants, none were classified as T2D. Mean BMI was 23.8 kg/m^2. FG was in the normal range (below prediabetic levels of 100 mg/dl) for most participants (91.2%) and mean FG was 88.44 mg/dl (SD = 9.78). Mean FI was 8.11 μUI/dl (SD = 5.57), and mean HOMA-IR was 1.80 (SD = 1.34). PCs of ancestry revealed admixture in the sample, with ancestry most closely resembling European (CEU), Colombian (CLM), Mexican American (MXL), and Puerto Rican (PUR) reference populations from the 1000 Genomes Project[35] (Figure 1).

3.2 | Genome-wide association study

We identified one novel locus with genome-wide significant evidence for association with FI (β = −0.299, SE = 0.054, p = 2.72×10^{-8}) at rs77465890 (effect allele frequency = 0.10) on chromosome 8, positioned within the CUB and Sushi Multiple Domains 1 and Sushi Multiple Domains 1 gene (*CSMD1*). We also identified 24 FG and 14 FI loci with suggestive evidence of association (p < 5×10^{-6}) (Table 2). The top variants for two of the suggestive FG loci (rs28589776 and rs147515244) were within the 1 Mb region of previously reported GWAS-significant variants (rs7708285[22] r^2 = 0.0009 and rs143399767[36] r^2 = 0.0007, respectively in the 1000 Genomes AMR population). Conditioning on these known variants did not materially change the effect estimates; β changed from −11.561 (p = 3.49×10^{-6}) to −11.351 (p = 5.00×10^{-6}) for rs28589776, and from 6.727 (p = 1.27×10^{-6}) to 6.724 (p = 1.29×10^{-6}) for rs147515244. Both rs28589776 and rs147515244 (Bonferroni-corrected significance level = 0.05/3383 = 1.48×10^{-5} and 0.05/3619 = 1.38×10^{-5}, respectively) represent significant evidence for allelic heterogeneity in well-known glucose loci. None of the top FI variants was within the 1 Mb region of previously reported GWAS-significant variants for these traits. HOMA-IR results are provided in the supplement (Table S1).

3.2.1 | Sensitivity analysis

Results from the main analysis remained similar after adjusting for BMIz (Table S2). No associations reached GWAS-significance; however, the GWAS-significant variant from the unadjusted analysis (rs77465890) remained the most significant variant for FI (β = −0.252, SE = 0.047, p = 1.03 × 10^{-7}) after BMIz adjustment. Three more of the FI variants were still suggestive after BMIz adjustment, and 15 additional FI variants achieved suggestive significance after BMIz adjustment that had not reached this threshold before adjustment. All 24 of the original suggestive FG variants and one additional variant were also suggestive for FG after BMIz adjustment. A well-known concern of adjustment for highly correlated variables is collider bias.[37,38] For this reason, analyses adjusting for BMIz should be interpreted with caution.

TABLE 2 Top independent signals in the Santiago Longitudinal Study for fasting glucose and fasting insulin

Trait	Gene/nearest gene*	SNP	CHR	BP	EA/OA	EAF	β	SE	p
GWAS-significant loci ($p < 5 \times 10^{-8}$)									
FI	*CSMD1*	rs77465890	8	3 628 570	C/T	0.10	−0.299	0.054	2.72E-8
Suggestive loci ($p < 5 \times 10^{-6}$)									
FG	*RP11-147G16.1**	rs10157848	1	82 996 068	C/G	0.96	7.241	1.578	4.00E-6
	LOC101927665	rs6748653	2	200 528 810	T/A	0.21	3.025	0.643	2.57E-6
	*AC010149.4**	rs113214710	2	231 442 593	T/G	0.07	−5.021	1.097	4.75E-6
	*AC009223.2**	rs138154342	2	41 452 492	G/A	0.01	−14.366	2.974	1.37E-6
	GBA3	rs79399931	4	22 714 327	A/C	0.02	−11.391	2.298	7.20E-7
	UCHL1-AS1	rs66475765	4	41 230 618	T/C	0.03	−8.212	1.770	3.51E-6
	CCSER1	rs79947031	4	91 829 969	C/T	0.11	4.110	0.882	3.19E-6
	*RP11-541P9.3**	rs189776108	5	162 420 388	T/C	0.05	5.880	1.283	4.63E-6
	ZBED3-AS1	rs28589776	5	76 406 470	T/C	0.01	−11.561	2.492	3.49E-6
	DCBLD1	rs117533208	6	117 855 911	C/T	0.02	10.537	2.289	4.14E-6
	MAN1A1	rs62418805	6	119 508 342	C/T	0.32	3.054	0.602	4.00E-7
	*AC004535.2**	rs141226872	7	10 748 548	G/A	0.01	12.042	2.622	4.38E-6
	*RPL7**	rs12546395	8	74 194 405	A/T	0.62	−2.569	0.533	1.46E-6
	SLC24A2	rs79818403	9	19 669 933	T/C	0.01	14.970	3.080	1.17E-6
	WNK2	rs147515244	9	96 046 087	A/T	0.05	6.727	1.389	1.27E-6
	*RP11-432B10.1**	rs7476984	10	109 170 924	A/G	0.40	2.826	0.540	1.65E-7
	*AL157931.1**	rs117292932	13	23 574 827	A/T	0.02	10.006	2.066	1.28E-6
	RTN4RL1	rs11656601	17	1 924 911	T/C	0.25	−3.509	0.731	1.56E-6
	ATP9B	rs7226934	18	76 904 665	C/T	0.16	3.354	0.729	4.21E-6
	*NLRP12**	rs139295665	19	54 336 151	A/G	0.01	−17.046	3.621	2.50E-6
	*RP11-560A15.4**	rs6092424	20	55 672 544	A/G	0.49	−2.659	0.534	6.22E-7
	*TAF4**	rs6061420	20	60 654 074	G/A	0.07	−6.014	1.274	2.35E-6
	*RP5-839B4.8**	rs80352176	20	9 952 118	G/A	0.09	−4.991	1.038	1.54E-6
	*PARVG**	rs139198	22	44 606 772	C/T	0.22	3.036	0.662	4.60E-6
FI	*NFIA*	rs7535730	1	61 871 356	G/A	0.18	0.225	0.046	1.00E-6
	NCKAP5	rs528181067	2	134 374 835	A/T	0.01	−0.776	0.164	2.31E-6
	IQCB1	rs2331964	3	121 542 898	C/T	0.67	0.166	0.036	4.14E-6
	*RP11-769 N22.1**	rs184687999	4	29 046 057	C/T	0.05	0.382	0.082	3.12E-6
	SPEF2	rs2361394	5	35 800 547	G/A	0.08	0.298	0.064	3.43E-6
	*CSMD1**	rs35051650	8	4 859 203	A/C	0.13	0.248	0.052	1.60E-6
	AKR1C3	rs117400599	10	5 143 717	G/T	0.04	0.443	0.091	1.27E-6
	PTPRO	rs7315300	12	15 610 293	A/T	0.24	0.207	0.040	2.12E-7
	RCOR1	rs12884198	14	103 155 465	A/G	0.02	0.801	0.147	5.58E-8
	LOC727924	rs181412737	15	22 367 512	C/T	0.01	0.766	0.167	4.35E-6
	*MCTP2**	rs12441824	15	94 738 631	A/G	0.48	−0.232	0.043	7.12E-8
	CNTNAP4	rs62051249	16	76 459 093	A/G	0.02	0.659	0.143	4.39E-6
	*TIAM1**	rs2833275	21	32 489 757	T/C	0.62	−0.170	0.037	4.45E-6
	*CTA-992D9.7**	rs4820743	22	27 512 801	T/C	0.78	0.189	0.041	4.71E-6

*Refers to the genes that the variant is near but not actually in. Abbreviations: BP, base pair position (hg19 build); CHR, chromosome; EA, effect allele; EAF, effect allele frequency; FG, fasting glucose; FI, fasting insulin; OA, other allele; p, p-value; SE, standard error; SNP, single nucleotide polymorphism; β, beta coefficient.

3.3 | Known loci generalizations

Table 3 reports the six variants that generalized from 78 known FG variants in 43 loci at nominal significance level ($p < 0.05$) and with a consistent direction of effect as previously reported. Two of these variants were positioned near one another in the glucose-6-phosphatase catalytic subunit 2 (*G6PC2*) gene on chromosome 2. No known variants for FI (out of 32 known FI variants in 22 loci)

TABLE 3 Loci reported in other studies to have GWAS-significant associations with fasting glucose that were generalized in the Santiago Longitudinal Study at nominal significance ($p < 0.05$) and with the same direction of effect

Gene/nearest gene*	SNP	PMID	CHR	BP	EA/OA	EAF	β	SE	p
G6PC2	rs492594	25625282[39]	2	169 764 176	C/G	0.60	1.262	0.545	0.021
	rs560887[a]	19060907,[40] 20081858,[29] 28270201,[36]	2	169 763 148	C/T	0.83	2.233	0.694	0.001
LOC101929710	rs6234	25625282,[39]	5	95 728 974	C/G	0.18	−1.627	0.730	0.026
GCK	rs2908290[b]	28905132,[21]	7	44 216 137	A/G	0.38	1.193	0.541	0.027
MTNR1B	rs10830963	20081858,[29]	11	92 708 710	G/C	0.20	1.685	0.681	0.013
*C2CD4B**	rs11071657	20081858,[29]	15	62 433 962	G/A	0.53	−1.106	0.540	0.041

Abbreviations: BP, base pair position (hg19 build); CHR, chromosome; EA, effect allele; EAF, effect allele frequency; OA, other allele; p, p-value; PMID, Pubmed ID for previously reported association; SE, standard error; SNP, single nucleotide polymorphism; β, beta coefficient.

*Refers to the genes that the variant is near but not actually in.

[a]Published findings for GWAS-significant associations for this SNP were inconsistent. One publication showed an opposite direction of effect from what we report in the table (PMID: 22581228[41]), and two others (PMID: 18451265[42] and 19060910[43]) reported the effect of a third allele (A) at this position instead of C or T.

[b]The direction of effect was consistent with the transethnic meta-analysis and in most population subgroups in this publication (AA, H/L and ASN) for this association, but opposite direction of effect from the AI/AN subgroup.

generalized in our cohort. Our look-up of all known FG and FI loci that did not generalize in our cohort is reported in Tables S3 and S4, respectively. While two of the FG variants (rs13387347 and rs13179048) reported in Table S3 displayed nominal statistical significance, the effect was directionally inconsistent.

3.4 | Validation results

Many of our top signals were not present at high enough allele counts in the MAGIC or NASH studies. We did observe directional consistency in 6 of 11 FG variants and 5 out of 9 FI variants that were available in these studies (Table S5). None of these results, however, was nominally significant.

We did not validate our genome-wide significant finding for the rs77465890 FI association in the PAGE study overall or by race/ethnicity stratified analyses (Table S6). Although we identified a directionally consistent effect in the African ancestry, Hispanic ancestry, and overall group (with and without BMI adjustment), these associations were not statistically significant. Because the HOMA-IR trait was not readily available in PAGE, we did not evaluate it for association with rs77465890.

4 | DISCUSSION

The discovery of genetic mechanisms influencing glycemic traits has the potential to identify important pathways to disease pathogenesis and therefore for disease prediction, prevention and treatment. Yet, the bulk of genetic epidemiological research has focused on European ancestry middle-aged adults, with very few genetic studies of ancestrally diverse, admixed populations.[44] It is important to include underrepresented groups in genetic studies, not only because they often have a higher disease or risk factor burden than their European ancestry counterparts, but also because they may have variants that are simply not present at high enough frequencies in European populations to detect meaningful associations. There is also little understanding of how genetic effects vary across the life-course. Although some studies have shown that the influence of genetic variation changes with age for other traits like leptin,[45] BMI,[46,47] and gene-environment interactions between physical activity and FI,[48] ours is the first study to our knowledge to identify a novel FI locus in a Chilean sample during adolescence.

Here, we demonstrate novel effects for glycemic traits in a young H/L population living in Chile, a country with high T2D prevalence. We identified a novel locus for FI with rs77465890 on chromosome 8. The effect allele for this SNP was present at a frequency of 0.10 in our study participants, comparable to that in the AMR population (0.11); the effect allele frequency was much lower in AFR (0.016) and EUR (0.0099) 1000 Genomes reference populations,[49] perhaps explaining why this variant's association with FI has not been previously identified. BMIz appeared to slightly attenuate this association (with β values changing by approximately 15% after BMIz adjustment). However, this SNP remained the most statistically significant signal for FI, showing that this association is not mediated by BMIz alone. Although we did not validate this locus in adult participants of the PAGE study with statistically significant results, we demonstrated directionally consistent β values in the Hispanic and African ancestry strata and overall PAGE group. Rs77465890 is positioned within an intronic region of *CSMD1*, a large gene spanning approximately 2 Mb.[50] The biological function of *CSMD1* is unclear; it has been associated with several diseases (including smallpox and benign adult familial myoclonic epilepsy), as well as potentially serving as a suppressor of squamous cell carcinomas, although evidence is conflicting.[50-53] Based on sequence orthology evidence from the Gene Ontology Resource, *CSMD1* may also be involved in glucose homeostasis.[54] Furthermore, *Csmd1* knockout mice display a complex neuropsychological phenotype also characterized by increased weight gain and lower glycemia after glucose challenges compared to wild-type mice.[55] This provides support for the biologic plausibility of our results

for this locus. Neither rs77465890 nor the 18 variants in highest LD with it (LD ≥ 0.6 in AMR populations in HaploReg v4.1[56]) were reported in the GTEx Portal to have any eQTL or splice QTL effects, although the majority of study participants are European ancestry in GTEx.[57]

In addition to the GWAS-significant variant in *CSMD1*, we identified several other variants that displayed suggestive evidence for an association with our traits. We also potentially identified novel secondary signals in two well-established loci for FG. Some of the suggestive SNPs are located in genes with potential biological relevance to our traits of interest. According to the GeneCards Human Gene Database, the Glucosylceramidase Beta 3 gene (*GBA3*) on chromosome 4 is involved in galactose metabolism pathways; the Solute Carrier Family 24 Member 2 gene (*SLC24A2*) and the WNK Lysine Deficient Protein Kinase 2 gene (*WNK2*) on chromosome 9, and the ATPase phospholipid transporting 9B gene (*ATP9B*) on chromosome 18 are involved in transport of glucose and other sugars.[50] Thus, replication for these suggestive signals is warranted. Interestingly, the variant on *ATP9B* was one of those showing the same β direction in the NASH validation.

Six associations for previously reported FG variants generalized in our cohort (Table 3). Although none was GWAS-significant, they displayed consistent direction of effect and may be involved in a biological process that affects the FG phenotype. In contrast, many of the published FG and FI SNPs did not generalize in our cohort at a nominal level of significance ($p < 0.05$). Our small sample size was most likely the deterministic factor, but other possible reasons include ancestry and/or age specific differences, and unique patterns of gene-gene and gene-environment effects.

The systematic evaluation of previously reported loci in our Chilean study revealed heterogeneity of allelic effects between H/L and European ancestry populations. We identified two FG loci with significant evidence for allelic heterogeneity. At the *WNK2* locus on chromosome 9, the A effect allele at rs147515244 is found at 5% frequency in our Chilean population and is monomorphic in all other populations listed in dbSNP.[58] This finding demonstrates the importance of GWAS discovery in ancestrally diverse populations, especially given that this locus is already known. In contrast, the T effect allele at rs28589776 is found at 1% in our Chilean data but is similarly rare in other reported populations in dbSNP (T allele in EUR = 2%; AFR = 3%).[58] Thus, given the rarity of this SNP, it would likely be missed by GWAS in Europeans as well. Taken together, the consideration of non-European populations in GWAS discovery is critical for us to obtain a more complete picture of the genetic architecture of glycemic traits.

Our sample size limited the power to detect the small effects that have been mapped for glycemic traits. Despite this limitation, we were able to generalize previously reported loci, identify novel secondary signals in known loci and identify a novel locus for FI. We were also limited to the glycemic traits that were measured (FG and FI) or derived from these traits (HOMA-IR). Including other phenotypes, such as 2-h plasma glucose as part of an oral glucose tolerance test, may have provided more comprehensive results but were not measured in the SLS. Another study limitation is that HOMA-IR, which is calculated from FG and FI measurements, is not necessarily a precise measurement of insulin resistance, since it cannot differentiate between increased secretion by pancreatic beta cells or decreased clearing of insulin, either of which could increase the HOMA-IR value.[59] However, HOMA-IR shows reasonably good correlations with insulin resistance indices derived from both oral and intravenous glucose challenges, or the euglycemic-hyperinsulinaemic clamp.[60] The euglycemic-hyperinsulinaemic clamp would provide more information but is more invasive and impractical in epidemiologic studies, was therefore not used in SLS participants. For this reason, our primary analysis considered two traits (FG and FI) but additionally provided HOMA-IR results in the supplement as a courtesy for those interested. The glycemic traits considered herein are a strength to our study in that they are clinically relevant, commonly utilized, and allowed for comparisons of our results to those of other studies. An important inclusion criterion for the original SLS parent study was birth weight > 3 kg; since low birthweight has been associated with increased risk of T2D later in life,[61] it is possible that excluding those infants with low birth weight could have affected our results.

In conclusion, our study of H/L adolescents identified a novel locus significantly associated with FI. Our study findings demonstrate the importance of expanding genetic epidemiological studies to include populations with diverse genetic ancestry that have been traditionally underrepresented in research. Since most GWAS focus on adults rather than adolescents, we also demonstrate the importance of including younger study populations that might show genetic effects that vary with age.

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CONFLICT OF INTEREST

Heather M Highland reports grants from NHLBI and American Diabetes Association during the conduct of the study, and personal feeds from the American Heart Association outside the submitted work. Xiuqing Guo, Kent D Taylor and Yii-Der Ida Chen report grants from the NIH during the conduct of this study. The other authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Victoria L Buchanan and Kari E North designed the study and drafted the initial manuscript; Estela Blanco, Sheila Gahagan, and Raquel Burrows collected the data; Anne E Justice, Mariaelisa Graff, and Yujie Wang carried out genetic data cleaning; Victoria L Buchanan, Mariaelisa Graff, and Yujie Wang conducted statistical analysis; Yujie Wang, Heather M Highland, Carolina Downie, Kari E North, Xiuqing Guo, Kent D Taylor, Yii-Der Ida Chen, Jie Yao and Jingyi Tan were involved in the validation studies; Victoria L Buchanan, Kari E North, Mariaelisa Graff and Anne E Justice were involved in interpretation of the results; all authors revised the manuscript and contributed to the content, and approved the submission and publication of the paper.

ORCID

Victoria L Buchanan https://orcid.org/0000-0001-9943-9950
Yujie Wang https://orcid.org/0000-0002-1087-2182
Estela Blanco https://orcid.org/0000-0002-6232-9210
Cecilia Albala https://orcid.org/0000-0002-6135-334X
Raquel Burrows https://orcid.org/0000-0001-9155-0689
José L Santos https://orcid.org/0000-0003-2895-0369
Bárbara Angel https://orcid.org/0000-0001-8773-5904
Betsy Lozoff https://orcid.org/0000-0002-0399-582X
Venkata Saroja Voruganti https://orcid.org/0000-0002-8704-4529
Kent D Taylor https://orcid.org/0000-0002-2756-4370
Carolina Downie https://orcid.org/0000-0001-6972-9981
Heather M Highland https://orcid.org/0000-0002-3583-8239
Anne E Justice https://orcid.org/0000-0002-8903-8712
Sheila Gahagan https://orcid.org/0000-0002-1105-7323
Kari E North https://orcid.org/0000-0002-8903-0366

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SUPPORTING INFORMATION

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