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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

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1 | ABSTRACT

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=2.72x10^{-8}) and was only slightly attenuated after adjusting for body mass index z-scores (β=-0.252, SE=0.047, p=1.03x10^{-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. *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 etiology.

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Abbreviations: T2D, type 2 diabetes; H/L, Hispanic/Latino; GWAS, genome-wide association study; FG, fasting glucose; FI, fasting insulin; HOMA-IR, homeostatic model assessment of insulin resistance; SLS, Santiago Longitudinal Study; BMIz, body mass index z-scores; MEGA, Multiethnic Genotyping Array; AMR, Admixed American reference panel; QC, quality control; SNP, single nucleotide polymorphism; PCs, principal components; LD, linkage disequilibrium; MAGIC, Meta-Analysis of Glucose and Insulin-related Traits Consortium; NASH, Nonalcoholic Steatohepatitis study; PAGE, Population Architecture using Genomics and Epidemiology Consortium; ARIC, Atherosclerosis Risk in Communities Study; CARDIA, Coronary Artery Risk Development in Young Adults Study; MEC, Multiethnic Cohort Study; HCHS/SOL, Hispanic

Community Health Study/ Study of Latinos; WHI, Women's Health Initiative; CHR, chromosome; BP, base pair position (hg19 build); EA/OA, effect allele/ other allele; EAF, effect allele frequency; SE, standard error.

2 | 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.

3 | METHODS

3.1 | 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 1,798 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 anemia. [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 measures, or the traits were unavailable for these individuals. This study has been approved by Institutional Review Boards (IRBs) 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.

3.2 | Trait measurements

3.2.1 | Glycemic traits

After fasting overnight for 8 to 12 hours before the adolescent visits occurring at age 16 to 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]:

$$\frac{\text{fasting insulin}(\mu IU/ml) \ * \ \text{fasting glucose}(\frac{mmol}{l})}{22.5}$$

3.2.2 | 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 (kg)/height^2 (m^2), then transformed into z-scores (BMIz) relative to Centers for Disease Control (CDC) anthropometric reference data (2007-2010). [19]

3.3 | 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 AMR (admixed American) reference panel. Quality control (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 ($p<5x10^{-8}$) 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]

3.4 | Statistical analysis

3.4.1 | 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 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]

3.4.2 | 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 directionaly consistent and nominally significant (p<0.05).

3.4.3 | Conditional analysis

To identify secondary signals in known loci, we evaluated any SNP-trait associations that displayed suggestive significance (p<5x10^{-6}) and were positioned within the 1Mb region (+/-500kb) 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 were defined using Bonferroni correction for the number of independent SNPs in each 1Mb interval of the evaluated loci (linkage disequilibrium (LD)-pruned at r^2<0.10) and provide evidence of allelic heterogeneity at known loci.

3.4.4 | 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 (HCHS/SOL), 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 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 standard errors 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*=7,683) ancestry and imputation information >0.8.

4 | RESULTS

4.1 | 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).

4.2 | 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=2.72x10^{-8}) at rs77465890 (effect allele frequency=0.10) on chromosome 8, positioned within the CUB and Sushi Multiple Domains 1 gene (*CSMD1*). We also identified 24 FG and 14 FI loci with suggestive evidence of association (p<5x10^{-6}) (Table 2). The top variants for two of the suggestive FG loci (rs28589776 and rs147515244) were within the 1Mb 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 reference population). Conditioning on these known variants did not materially change the effect estimates; β changed from -11.561 (p=3.49x10^{-6}) to -11.351 (p=5.00x10^{-6}) for rs28589776, and from 6.727 (p=1.27x10^{-6}) to 6.724 (p=1.29x10^{-6}) for rs147515244. Both rs28589776 and rs147515244 (Bonferroni-corrected

siginificance level=0.05/3,383=1.48x10^{-5} and 0.05/3,619=1.38x10^{-5}, respectively) represent significant evidence for allelic heterogeneity in well-known glucose loci. None of the top FI variants were within the 1Mb region of previously reported GWAS-significant variants for these traits. HOMA-IR results are provided in the supplement (Table S1).

4.2.1 | 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=1.03x10^{-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.

4.3 | 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) 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.

4.4 | 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, were 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.

5 | 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] body mass index, [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 reference 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 2Mb. [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 linkage disequilibrium (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 were 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-hour 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-hyperinsulinemic clamp. [60] The euglycemic-hyperinsulinemic 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 >3kg; 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.

6 | CONFLICTS OF INTEREST STATEMENT:

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VLB and KEN designed the study and drafted the initial manuscript; EB, SG, and RB collected the data; AEJ, MG, and YW carried out genetic data cleaning; VLB, MG, and YW conducted statistical analysis; YW, HMH, CD, KEN, XG, KDT, YDIC, JY, and JT were involved in the validation studies; VLB, KEN, MG, and AEJ 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. We would like to thank the participants and their family members from the Santiago Longitudinal Study.

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9 | SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article. Table S1, Table S2, Table S3, Table S4, Table S5, Table S6

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 x insulin/405)	1.80 (1.34)

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

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 ($p<5x10^{-8}$)								
FI	*CSMD1*	rs77465890	8	3628570	C/T	0.10	-0.299	0.054	2.72E-8
	Suggestive loci ($p<5x10^{-6}$)								
FG	*RP11-147G16.1**	rs10157848	1	82996068	C/G	0.96	7.241	1.578	4.00E-6
	LOC101927665	rs6748653	2	200528810	T/A	0.21	3.025	0.643	2.57E-6
	*AC010149.4**	rs113214710	2	231442593	T/G	0.07	-5.021	1.097	4.75E-6
	*AC009223.2**	rs138154342	2	41452492	G/A	0.01	-14.366	2.974	1.37E-6
	GBA3	rs79399931	4	22714327	A/C	0.02	-11.391	2.298	7.20E-7
	UCHL1-AS1	rs66475765	4	41230618	T/C	0.03	-8.212	1.770	3.51E-6
	CCSER1	rs79947031	4	91829969	C/T	0.11	4.110	0.882	3.19E-6
	*RP11-541P9.3**	rs189776108	5	162420388	T/C	0.05	5.880	1.283	4.63E-6
	ZBED3-AS1	rs28589776	5	76406470	T/C	0.01	-11.561	2.492	3.49E-6
	DCBLD1	rs117533208	6	117855911	C/T	0.02	10.537	2.289	4.14E-6
	MAN1A1	rs62418805	6	119508342	C/T	0.32	3.054	0.602	4.00E-7
	*AC004535.2**	rs141226872	7	10748548	G/A	0.01	12.042	2.622	4.38E-6
	*RPL7**	rs12546395	8	74194405	A/T	0.62	-2.569	0.533	1.46E-6
	SLC24A2	rs79818403	9	19669933	T/C	0.01	14.970	3.080	1.17E-6
	WNK2	rs147515244	9	96046087	A/T	0.05	6.727	1.389	1.27E-6
	*RP11-432B10.1**	rs7476984	10	109170924	A/G	0.40	2.826	0.540	1.65E-7
	*AL157931.1**	rs117292932	13	23574827	A/T	0.02	10.006	2.066	1.28E-6
	RTN4RL1	rs11656601	17	1924911	T/C	0.25	-3.509	0.731	1.56E-6
	ATP9B	rs7226934	18	76904665	C/T	0.16	3.354	0.729	4.21E-6
	*NLRP12**	rs139295665	19	54336151	A/G	0.01	-17.046	3.621	2.50E-6
	*RP11-560A15.4**	rs6092424	20	55672544	A/G	0.49	-2.659	0.534	6.22E-7
	*TAF4**	rs6061420	20	60654074	G/A	0.07	-6.014	1.274	2.35E-6
	*RP5-839B4.8**	rs80352176	20	9952118	G/A	0.09	-4.991	1.038	1.54E-6
	*PARVG**	rs139198	22	44606772	C/T	0.22	3.036	0.662	4.60E-6
FI	*NFIA*	rs7535730	1	61871356	G/A	0.18	0.225	0.046	1.00E-6
	NCKAP5	rs528181067	2	134374835	A/T	0.01	-0.776	0.164	2.31E-6
	IQCB1	rs2331964	3	121542898	C/T	0.67	0.166	0.036	4.14E-6
	*RP11-769N22.1**	rs184687999	4	29046057	C/T	0.05	0.382	0.082	3.12E-6
	SPEF2	rs2361394	5	35800547	G/A	0.08	0.298	0.064	3.43E-6
	*CSMD1**	rs35051650	8	4859203	A/C	0.13	0.248	0.052	1.60E-6
	AKR1C3	rs117400599	10	5143717	G/T	0.04	0.443	0.091	1.27E-6
	PTPRO	rs7315300	12	15610293	A/T	0.24	0.207	0.040	2.12E-7
	RCOR1	rs12884198	14	103155465	A/G	0.02	0.801	0.147	5.58E-8
	LOC727924	rs181412737	15	22367512	C/T	0.01	0.766	0.167	4.35E-6
	*MCTP2**	rs12441824	15	94738631	A/G	0.48	-0.232	0.043	7.12E-8
	CNTNAP4	rs62051249	16	76459093	A/G	0.02	0.659	0.143	4.39E-6
	*TIAM1**	rs2833275	21	32489757	T/C	0.62	-0.170	0.037	4.45E-6
	*CTA-992D9.7**	rs4820743	22	27512801	T/C	0.78	0.189	0.041	4.71E-6

Abbreviations: SNP, single nucleotide polymorphism; CHR, chromosome; BP, base pair position (hg19 build); EA, effect allele; OA, other allele; EAF, effect allele frequency; *β*, beta coefficient; SE, standard error; *p*, p-value; FG, fasting glucose; FI, fasting insulin.

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	169764176	C/G	0.60	1.262	0.545	0.021
	rs560887[a]	19060907,[40] 20081858,[29] 28270201,[36]	2	169763148	C/T	0.83	2.233	0.694	0.001
LOC101929710	rs6234	25625282,[39]	5	95728974	C/G	0.18	-1.627	0.730	0.026
GCK	rs2908290[b]	28905132,[21]	7	44216137	A/G	0.38	1.193	0.541	0.027
MTNR1B	rs10830963	20081858,[29]	11	92708710	G/C	0.20	1.685	0.681	0.013
*C2CD4B**	rs11071657	20081858,[29]	15	62433962	G/A	0.53	-1.106	0.540	0.041

[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.

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

Table and figure legends:

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

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).

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

Abbreviations: SNP, single nucleotide polymorphism; CHR, chromosome; BP, base pair position (hg19 build); EA, effect allele; OA, other allele; EAF, effect allele frequency; *β*, beta coefficient; SE, standard error; *P*, p-value; FG, fasting glucose; FI, fasting insulin; HOMA-IR, homeostatic model assessment of insulin resistance.

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

[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.

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

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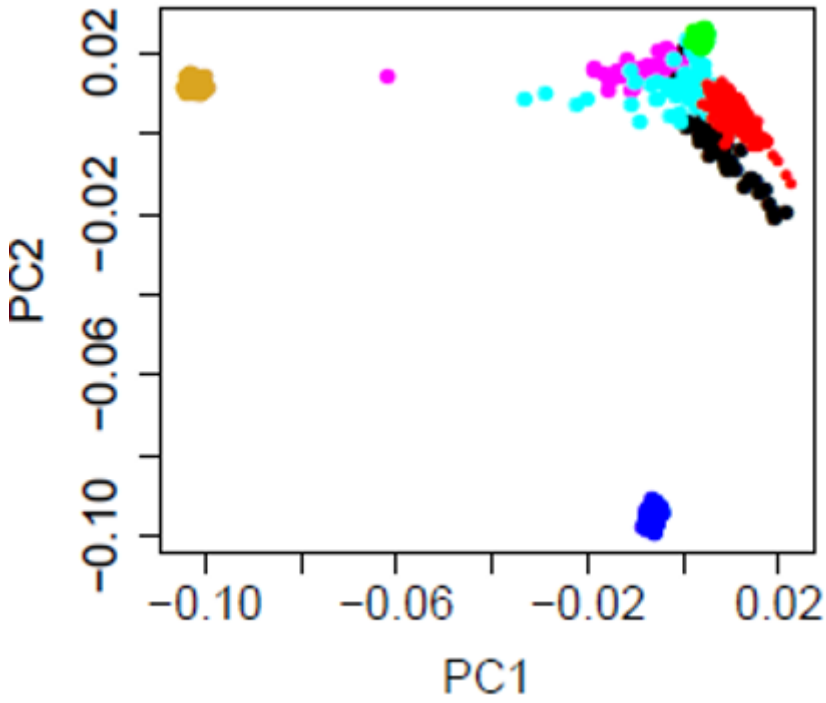

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Genome-wide association study identifying novel variant for fasting insulin and allelic heterogeneity in known glycemic loci in Chilean adolescents: The Santiago Longitudinal Study

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9 | SUPPORTING INFORMATION

TABLE S1 Top independent signals in the Santiago Longitudinal Study for homeostatic model of insulin resistance

Gene/ Nearest gene*	SNP	CHR	BP	EA/OA	EAF	*β*	SE	*p*
GWAS-significant loci ($p<5x10^{-8}$)								
CSMD1	rs77465890	8	3628570	C/T	0.10	-0.322	0.057	1.66E-8
Suggestive loci ($p<5x10^{-6}$)								
*RP11-191N8.2**	rs35726538	1	221976039	G/A	0.02	0.693	0.142	1.16E-6
NFIA	rs7535730	1	61871356	G/A	0.18	0.236	0.049	1.50E-6
NCKAP5	rs528181067	2	134374835	A/T	0.01	-0.823	0.175	2.52E-6
*RP11-769N22.1**	rs184687999	4	29046057	C/T	0.05	0.415	0.087	1.86E-6
SPEF2	rs2361393	5	35800504	G/A	0.19	0.224	0.047	1.58E-6
*MCM9**	rs117381875	6	119134465	C/T	0.02	0.689	0.141	1.12E-6
*CSMD1**	rs35051650	8	4859203	A/C	0.13	0.269	0.055	9.49E-7
KIAA1217	rs143654218	10	24319915	G/A	0.01	0.968	0.206	2.54E-6
AKR1C3	rs117400599	10	5143717	G/T	0.04	0.467	0.097	1.55E-6
PTPRO	rs7315300	12	15610293	A/T	0.24	0.223	0.042	1.46E-7
RCOR1	rs12884198	14	103155465	A/G	0.02	0.831	0.157	1.23E-7
*MCTP2**	rs12441824	15	94738631	A/G	0.48	-0.240	0.046	1.69E-7
DCC	rs9950187	18	50636401	T/A	0.04	0.453	0.095	1.95E-6
*CTA-992D9.7**	rs4820743	22	27512801	T/C	0.78	0.207	0.044	2.26E-6

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

TABLE S2 Top independent signals in the Santiago Longitudinal Study for fasting glucose, fasting insulin, and homeostatic model assessment of insulin resistance, adjusted for CDC pediatric z-scores of body mass index.

Trait	Gene/ Nearest Gene*	SNP	CHR	BP	EA/OA	EAF	*β*	SE	*p*
FG	*RP11-147G16.1**	rs10157848	1	82996068	C/G	0.96	7.233	1.579	5.00E-6
	LOC101927665	rs6748653	2	200528810	T/A	0.21	3.023	0.643	2.60E-6
	*AC010149.4**	rs113214710	2	231442593	T/G	0.07	-5.069	1.100	4.03E-6
	*AC009223.2**	rs138154342	2	41452492	G/A	0.01	-14.391	2.975	1.31E-6
	TXNRD3	rs78870998	3	126352111	C/A	0.03	7.859	1.719	4.85E-6
	GBA3	rs79399931	4	22714327	A/C	0.02	-11.381	2.300	7.46E-7
	UCHL1-AS1	rs66475765	4	41230618	T/C	0.03	-8.210	1.770	3.53E-6
	CCSER1	rs79947031	4	91829969	C/T	0.11	4.108	0.882	3.22E-6
	*RP11-541P9.3**	rs189776108	5	162420388	T/C	0.05	5.905	1.284	4.26E-6
	ZBED3-AS1	rs28589776	5	76406470	T/C	0.01	-11.552	2.492	3.56E-6
	DCBLD1	rs117533208	6	117855911	C/T	0.02	10.528	2.291	4.32E-6
	MAN1A1	rs62418805	6	119508342	C/T	0.32	3.055	0.604	4.19E-7
	*AC004535.2**	rs141226872	7	10748548	G/A	0.01	12.046	2.622	4.34E-6
	*RPL7**	rs12546395	8	74194405	A/T	0.62	-2.573	0.533	1.40E-6
	SLC24A2	rs79818403	9	19669933	T/C	0.01	15.296	3.100	8.06E-7
	WNK2	rs147515244	9	96046087	A/T	0.05	6.730	1.389	1.26E-6
	*RP11-432B10.1**	rs7476984	10	109170924	A/G	0.40	2.825	0.540	1.72E-7
	*AL157931.1**	rs117292932	13	23574827	A/T	0.02	9.998	2.067	1.31E-6
	RTN4RL1	rs11656601	17	1924911	T/C	0.25	-3.534	0.732	1.36E-6
	ATP9B	rs7226934	18	76904665	C/T	0.16	3.377	0.730	3.74E-6
	*NLRP12**	rs139295665	19	54336151	A/G	0.01	-17.044	3.620	2.50E-6
	*RP11-560A15.4**	rs6092424	20	55672544	A/G	0.49	-2.667	0.534	5.82E-7
	*TAF4**	rs6061420	20	60654074	G/A	0.07	-6.021	1.274	2.29E-6
	*RP5-839B4.8**	rs80352176	20	9952118	G/A	0.09	-4.994	1.038	1.52E-6
	*PARVG**	rs139198	22	44606772	C/T	0.22	3.040	0.662	4.47E-6
FI	*ENSA**	rs115406107	1	150594155	A/T	0.02	0.508	0.105	1.00E-6
	KAZN	rs80204739	1	15065485	G/C	0.02	0.580	0.127	5.00E-6
	*PLD5**	rs61839743	1	242873445	C/T	0.01	-0.883	0.185	2.00E-6
	SMEK2	rs60356354	2	55833911	C/T	0.03	-0.452	0.095	2.06E-6
	LINC00290	rs6831952	4	182066235	T/G	0.67	0.164	0.035	3.04E-6
	*RP11-434D11.4**	rs1546499	5	126033156	C/A	0.43	0.146	0.031	2.13E-6
	SPEF2	rs2361394	5	35800547	G/A	0.08	0.287	0.056	2.80E-7
	*RP11-744I24.2**	rs7795885	7	141251044	G/C	0.03	0.427	0.093	4.20E-6
	DOCK5	rs2709613	8	25212994	C/G	0.97	0.474	0.101	3.03E-6
	CSMD1	rs77465890	8	3628570	C/T	0.10	-0.252	0.047	1.03E-7
	*CSMD1**	rs34371265	8	4859170	C/T	0.13	0.216	0.045	1.82E-6
	*PRAG1**	rs577483743	8	8376874	A/T	0.02	-0.516	0.111	3.61E-6
	*AL157884.1**	rs12337921	9	32735066	A/G	0.02	-0.550	0.117	2.61E-6
	*CTD-2507G9.1**	rs11029253	11	26163242	A/T	0.09	0.268	0.058	3.04E-6
	RCOR1	rs12884198	14	103155465	A/G	0.02	0.663	0.130	3.28E-7
	MAP4K5	rs77026144	14	50937785	T/C	0.01	0.942	0.187	4.80E-7
	CIITA	rs45513895	16	10995145	C/T	0.03	-0.419	0.088	2.12E-6
	APBA3	rs10460192	19	3756197	C/T	0.77	0.172	0.037	4.24E-6
	PLXNB2	rs62241209	22	50734392	A/G	0.15	0.213	0.045	2.59E-6
HOMA-IR	*ENSA**	rs115406107	1	150594155	A/T	0.02	0.537	0.114	2.00E-6
	KAZN	rs80204739	1	15065485	G/C	0.02	0.643	0.137	3.00E-6
	NFIA	rs2499526	1	61870696	T/C	0.55	-0.150	0.033	4.00E-6
	*RP11-434D11.4**	rs1546499	5	126033156	C/A	0.43	0.153	0.033	4.02E-6
	SPEF2	rs2361394	5	35800547	G/A	0.08	0.305	0.060	4.52E-7
	*MCM9**	rs117381875	6	119134465	C/T	0.02	0.594	0.126	2.48E-6
	CSMD1	rs77465890	8	3628570	C/T	0.10	-0.275	0.051	7.11E-8
	*CSMD1**	rs34371265	8	4859170	C/T	0.13	0.237	0.049	1.21E-6
	*PRAG1**	rs577483743	8	8376874	A/T	0.02	-0.554	0.120	4.09E-6
	*CTD-2507G9.1**	rs1489506	11	26126773	A/C	0.10	0.258	0.056	4.73E-6
	RCOR1	rs12884198	14	103155465	A/G	0.02	0.692	0.140	8.41E-7
	MAP4K5	rs77026144	14	50937785	T/C	0.01	1.054	0.202	1.75E-7
	*RP11-66B24.5**	rs149208997	15	101334196	T/C	0.01	-0.931	0.200	3.44E-6
	DNAH17	rs1530433	17	76559768	C/T	0.56	-0.161	0.033	1.44E-6
	APBA3	rs10460192	19	3756197	C/T	0.77	0.193	0.040	1.59E-6
	PLXNB2	rs62241209	22	50734392	A/G	0.15	0.228	0.049	3.08E-6

Abbreviations: SNP, single nucleotide polymorphism; CHR, chromosome; BP, base pair position (hg19 build); EA, effect allele; OA, other allele; EAF, effect allele frequency; *β*, beta coefficient; SE, standard error; *p*, p-value; FG, fasting glucose; FI, fasting insulin; HOMA-IR, homeostatic model assessment of insulin resistance.

TABLE S3 Loci reported in other studies to have GWAS-significant associations with fasting glucose that did not generalize in the Santiago Longitudinal Study. Associations either did not reach the nominal significance threshold of $p<0.05$ or showed a direction of effect inconsistent with other studies. p-values for nominally significant associations are bolded.

Gene/ nearest gene*	SNP	PMID	CHR	BP	EA/ OA	EAF	β	SE	p	Direction of effect consistent with other studies?
	rs79687284	28270201 [1]	1	214150821	C/G	0.02	3.430	2.503	0.171	Yes
PROX1-AS1	rs340874	20081858 [2], 22581228 [3]	1	214159256	C/T	0.39	-0.350	0.579	0.545	No
*Metazoa_SRP**	rs17407594	25223902 [4]	1	66170362	A/G	0.19	0.442	0.798	0.541	Yes
	rs477224	28905132 [5]	2	169750483	T/C	0.73	-0.550	0.627	0.381	Different alleles (EA/OA:A/G) reported in other study.
*SPC25**	rs13387347	25187374 [6]	2	169754846	C/T	0.38	-1.346	0.555	**0.015**	No
*AC018712.3**	rs733331	25187374 [6]	2	173546313	A/G	0.13	-0.580	0.804	0.470	No
DPYSL5	rs1371614	22581228 [3]	2	27152874	T/C	0.38	-0.250	0.546	0.647	No
	rs780095	28270201 [1]	2	27741105	G/A	0.64	0.226	0.564	0.689	Yes
GCKR	rs780094	20081858 [2], 22581228 [3], 25187374 [6]	2	27741237	C/T	0.67	-0.091	0.574	0.874	Other studies inconsistent with one another.
MRPL33	rs3736594	22581228 [3]	2	27995781	C/A	0.60	0.154	0.544	0.777	No
*AC012354.6**	rs895636	25187374 [6]	2	45188353	T/C	0.27	-0.703	0.614	0.252	No
ADCY5	rs11708067	20081858 [2], 22581228 [3]	3	123065778	G/A	0.28	-0.410	0.582	0.482	Yes
	rs11920090	20081858 [2], 22581228 [3]	3	170717521	A/T	0.11	-0.332	0.886	0.708	Other studies inconsistent with one another.
	rs8192675	28270201 [1]	3	170724883	C/T	0.34	-0.191	0.575	0.740	No
SLC2A2	rs9873618	28270201 [1]	3	170733076	A/G	0.33	-0.342	0.577	0.554	No
IGF2BP2	rs7651090	22885924 [7]	3	185513392	G/A	0.32	0.025	0.578	0.965	Yes
AMT	rs11715915	22885924 [7]	3	49455330	T/C	0.16	-0.508	0.730	0.486	Yes
ZBED3-AS1	rs7708285	22885924 [7]	5	76425867	A/G	0.69	-0.850	0.594	0.152	Yes
	rs4869272	22885924 [7]	5	95539448	T/C	0.81	1.195	0.702	0.089	Yes
LOC101929710	rs13179048	22581228 [3]	5	95542726	A/C	0.18	-1.427	0.714	**0.046**	No
CDKAL1	rs9356744	25187374 [6]	6	20685486	C/T	0.27	-0.235	0.596	0.694	No
	rs17762454	22885924 [7]	6	7213200	T/C	0.40	0.109	0.569	0.849	Yes
RREB1	rs35742417	25625282 [8]	6	7247344	A/C	0.06	-0.723	1.148	0.529	Yes
	rs2191349	20081858 [2], 22581228 [3]	7	15064309	T/G	0.39	0.581	0.559	0.298	Yes
*AC006458.3**	rs1974620	25187374 [6]	7	15065467	T/C	0.39	0.578	0.559	0.301	Yes
	rs10259649	26132169 [9]	7	44219705	C/T	0.24	0.597	0.632	0.345	Yes
GCK	rs730497	25187374 [6]	7	44223721	A/G	0.18	0.506	0.698	0.469	Yes
	rs1799884	23575436 [10]	7	44229068	T/C	0.18	0.446	0.697	0.523	Different effect allele (EA:A) reported in other study.
*GCK**	rs4607517	19060907 [11], 20081858 [2], 22581228 [3]	7	44235668	A/G	0.18	0.428	0.699	0.540	Yes
YKT6	rs917793	28270201 [1]	7	44245853	T/A	0.29	-0.070	0.602	0.908	No
*CAMK2B**	rs878521	26132169 [9]	7	44255643	A/G	0.33	0.264	0.574	0.645	Yes
	rs10248619	22581228 [3]	7	50751090	C/T	0.78	-0.514	0.641	0.422	Yes
GRB10	rs6943153	22885924 [7]	7	50791579	C/T	0.56	-0.765	0.560	0.172	Yes
	rs13266634	28270201 [1]	8	118184783	T/C	0.21	-1.069	0.637	0.094	No
	rs3802177	25187374 [6]	8	118185025	A/G	0.21	-1.097	0.637	0.085	Yes
SLC30A8	rs11558471	20081858 [2], 21873549 [12], 22581228 [3], 28270201 [1]	8	118185733	G/A	0.22	-1.165	0.623	0.062	Other studies inconsistent with one another.
*RP11-115J16.1**	rs983309	22885924 [7]	8	9177732	G/T	0.78	-0.682	0.634	0.282	Yes
LOC157273	rs4841132	22581228 [3]	8	9183596	G/A	0.79	-0.459	0.662	0.488	Yes
*ABO**	rs651007	25631608 [13]	9	136153875	T/C	0.15	0.494	0.748	0.509	Different alleles (EA/OA:A/G) reported in other study.
DNLZ	rs3829109	22885924 [7]	9	139256766	A/G	0.43	-1.006	0.541	0.063	Yes
*CDKN2B-AS1**	rs10811661	25187374 [6]	9	22134094	C/T	0.14	0.468	0.780	0.548	No
	rs7034200	20081858 [2]	9	4289050	A/C	0.53	0.768	0.573	0.180	Yes
GLIS3	rs4237150	25187374 [6]	9	4290085	C/G	0.47	0.783	0.569	0.169	Yes
KANK1	rs10815355	25187374 [6]	9	622523	T/G	0.06	-0.149	1.167	0.898	No
*RP11-381K7.1**	rs10885122	20081858 [2]	10	113042093	G/T	0.86	-0.378	0.798	0.636	No
	rs4506565	20081858 [2]	10	114756041	T/A	0.24	-0.431	0.662	0.515	No
	rs7903146	21873549 [12]	10	114758349	T/C	0.24	-0.227	0.664	0.733	No
TCF7L2	rs12243326	22581228 [3]	10	114788815	C/T	0.21	-0.035	0.678	0.959	Yes

CRY2	rs11605924	20081858 [2], 22581228 [3]	11	45873091	C/A	0.57	-0.122	0.526	0.817	Yes
MADD	rs7944584	20081858 [2], 22581228 [3]	11	47336320	T/A	0.19	0.672	0.676	0.320	No
*OR4S1**	rs1483121	22581228 [3]	11	48333360	A/G	0.08	0.139	1.000	0.890	Yes
FADS1	rs174550	20081858 [2], 22581228 [3]	11	61571478	C/T	0.62	0.060	0.566	0.915	No
ARAP1	rs11603334	22581228 [3]	11	72432985	A/G	0.07	-1.506	1.078	0.162	No
	rs3847554	25187374 [6]	11	92668826	T/C	0.29	0.590	0.597	0.322	Yes
	rs1387153	19060909 [14]	11	92673828	T/C	0.21	1.251	0.664	0.059	Yes
	rs7936247	23903356 [15]	11	92690032	T/G	0.24	1.054	0.622	0.090	Yes
	rs2166706	19651812 [16]	11	92691532	C/T	0.27	1.046	0.610	0.086	Different alleles (EA/OA:G/A) reported in other study.
*RP11-676F20.1**	rs10830962	23575436 [10]	11	92698427	G/C	0.29	0.806	0.598	0.178	No
*RP11-503G7.2**	rs10747083	22885924 [7]	12	133041618	A/G	0.72	-0.163	0.588	0.782	No
GLS2	rs2657879	22885924 [7]	12	56865338	G/A	0.22	0.501	0.642	0.435	Yes
RMST	rs17331697	26132169 [9]	12	97868906	C/T	0.04	-0.365	1.291	0.777	Yes
*PDX1-AS1**	rs2293941	22581228 [3]	13	28491198	A/G	0.33	1.071	0.578	0.064	Yes
PDX1	rs7981781	28270201 [1]	13	28499962	A/G	0.33	1.136	0.610	0.063	Yes
WARS	rs3783347	22885924 [7]	14	100839261	T/G	0.11	-0.566	0.861	0.511	Yes
*C2CD4A**	rs7173964	22581228 [3]	15	62396942	A/G	0.48	-0.073	0.538	0.892	No
IGF1R	rs2018860	25187374 [6]	15	99258710	T/A	0.54	-0.528	0.548	0.336	Yes
QPCTL	rs2302593	22885924 [7]	19	46196634	G/C	0.52	0.693	0.545	0.204	No
LINC00261	rs6113722	22885924 [7]	20	22557099	A/G	0.04	1.144	1.444	0.428	No
*LINC00261**	rs6048205	22581228 [3]	20	22559601	G/A	0.04	0.269	1.374	0.845	No
*RP4-788L20.3**	rs1209523	20152958 [17]	20	22567942	T/C	0.03	1.741	1.577	0.269	No
LOC101929685	rs6048216	25187374 [6]	20	22581268	C/T	0.04	1.265	1.371	0.356	No
TOP1	rs6072275	22885924 [7]	20	39743905	A/G	0.14	0.753	0.805	0.349	Yes

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

TABLE S4 Loci reported in other studies to have GWAS-significant associations with fasting insulin that did not generalize in the Santiago Longitudinal Study. No associations reached the nominal significance threshold of $p<0.05$ for this trait.

Gene/ nearest gene*	SNP	PMID	CHR	BP	EA/ OA	EAF	β	SE	p	Direction of effect consistent with other studies?
*RP11-95P13.1**	rs2820436	22885924 [7]	1	219640680	C/A	0.51	0.044	0.034	0.193	Yes
	rs2785980	22581228 [3]	1	219700519	C/T	0.54	-0.009	0.036	0.794	Yes
*RP11-95P13.2**	rs4846565	22885924 [7]	1	219722104	A/G	0.54	0.018	0.035	0.612	No
MAP3K19	rs1530559	22885924 [7]	2	135755629	G/A	0.68	0.005	0.042	0.911	No
LOC101929615	rs10195252	22885924 [7]	2	165513091	C/T	0.22	0.024	0.044	0.592	No
COBLL1	rs7607980	22581228 [3]	2	165551201	C/T	0.07	-0.008	0.068	0.910	Yes
	rs2943634	22581228 [3]	2	227068080	C/A	0.83	0.022	0.047	0.643	No
*AC068138.1**	rs2943645	22885924 [7]	2	227099180	T/C	0.82	0.038	0.045	0.399	Yes
GCKR	rs780094	20081858 [2], 22581228 [3]	2	27741237	C/T	0.67	0.062	0.036	0.089	Other studies inconsistent with one another.
*AY269186.2**	rs9841287	22581228 [3]	3	108993	G/A	0.34	-0.034	0.036	0.338	Yes
PPARG	rs17036328	22885924 [7]	3	12390484	C/T	0.12	-0.016	0.054	0.775	Yes
	rs974801	22885924 [7]	4	106071064	G/A	0.38	0.001	0.036	0.970	Yes
TET2	rs9884482	22885924 [7]	4	106081636	C/T	0.38	-0.006	0.036	0.866	No
	rs4691380	22581228 [3]	4	157720124	T/C	0.35	0.038	0.035	0.283	Yes
PDGFC	rs6822892	22885924 [7]	4	157734675	G/A	0.35	0.041	0.035	0.244	No
MSMO1	rs17046216	22791750 [18]	4	166255704	A/T	0.21	0.049	0.044	0.264	Yes
FAM13A	rs3822072	22885924 [7]	4	89741269	A/G	0.38	0.008	0.036	0.823	Yes
ARL15	rs4865796	22885924 [7]	5	53272664	A/G	0.84	-0.023	0.049	0.645	No
*AC022431.2**	rs459193	22885924 [7]	5	55806751	G/A	0.79	0.042	0.042	0.320	Yes
RSPO3	rs2745353	22885924 [7]	6	127452935	T/C	0.61	-0.009	0.036	0.802	No
UHRF1BP1	rs6912327	22885924 [7]	6	34764922	C/T	0.24	0.059	0.039	0.131	No
*UHRF1BP1**	rs4646949	22581228 [3]	6	34845449	G/T	0.38	0.033	0.035	0.337	No
HIP1	rs1167800	22885924 [7]	7	75176196	A/G	0.61	-0.006	0.037	0.880	No
*RP11-115J16.1**	rs983309	22885924 [7]	8	9177732	G/T	0.78	-0.059	0.040	0.141	Yes
	rs4841132	22581228 [3]	8	9183596	G/A	0.79	-0.066	0.042	0.115	Yes
LOC157273	rs2126259	22885924 [7]	8	9185146	C/T	0.73	-0.031	0.039	0.419	Yes
TCF7L2	rs7903146	22581228, [3] 22885924[7]	10	114758349	T/C	0.24	-0.016	0.042	0.701	Other studies inconsistent with one another.
*MIR378C**	rs7077836	22791750 [18]	10	132751498	A/G	0.11	0.007	0.055	0.896	Different effect allele (EA:T) reported in other study.
IGF1	rs35767	20081858 [2]	12	102875569	G/A	0.84	0.038	0.049	0.433	Yes
*IGF1**	rs35747	22581228 [3]	12	102912558	A/G	0.83	0.035	0.048	0.463	Yes
FTO	rs1421085	22885924 [7]	16	53800954	C/T	0.23	0.063	0.041	0.122	Yes
PEPD	rs731839	22885924 [7]	19	33899065	A/G	0.65	0.035	0.036	0.322	No

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

TABLE S5 Meta-Analyses of Glucose and Insulin-Related Traits Consortium (MAGIC) and Nonalcoholic Steatohepatitis (NASH) validation results for top independent fasting glucose, fasting insulin, and homeostatic model of insulin resistance results. Variants with minor allele count <10 in these studies not shown.

						MAGIC						NASH					
	Gene/ Nearest gene*	SNP	CHR	BP	EA/ OA	EAF	*β*	SE	*p*	*n*	Consist. direction of effect?	EAF	*β*	SE	*p*	*n*	Consist. direction of effect?
FG	*LOC101927665*	rs6748653	2	200528810	T/A	--	--	--	--	--	--	0.12	1.616	1.393	0.247	207	Yes
	*AC010149.4**	rs113214710	2	231442593	T/G	--	--	--	--	--	--	0.05	0.983	1.969	0.618	207	No
	CCSER1	rs79947031	4	91829969	C/T	--	--	--	--	--	--	0.13	0.802	1.270	0.529	207	Yes
	MAN1A1	rs62418805	6	119508342	C/T	--	--	--	--	--	--	0.28	-0.066	1.079	0.951	207	No
	*RPL7**	rs12546395	8	74194405	A/T	--	--	--	--	--	--	0.68	0.212	0.981	0.829	207	No
	*RP11-432B10.1**	rs7476984	10	109170924	A/G	--	--	--	--	--	--	0.38	0.355	0.927	0.702	207	Yes
	RTN4RL1	rs11656601	17	1924911	T/C	--	--	--	--	--	--	0.23	0.253	1.103	0.819	207	No
	ATP9B	rs7226934	18	76904665	C/T	--	--	--	--	--	--	0.19	1.847	1.145	0.108	207	Yes
	*RP5-839B4.8**	rs80352176	20	9952118	G/A	--	--	--	--	--	--	0.12	-0.486	1.362	0.722	207	Yes
	*RP11-560A15.4**	rs6092424	20	55672544	A/G	--	--	--	--	--	--	0.41	-0.180	0.878	0.837	207	Yes
	*PARVG**	rs139198	22	44606772	C/T	--	--	--	--	--	--	0.20	-0.073	1.117	0.948	207	No
FI	*NFIA*	rs7535730	1	61871356	G/A	0.78	0.003	0.005	0.501	38,238	Yes	0.18	0.005	0.112	0.967	201	Yes
	IQCB1	rs2331964	3	121542898	C/T	0.66	-0.004	0.004	0.295	38,238	No	0.26	0.016	0.098	0.871	201	Yes
	SPEF2	rs2361394	5	35800547	G/A	0.94	-0.003	0.009	0.768	38,238	No	0.07	-0.166	0.164	0.312	201	No
	CSMD1	rs77465890	8	3628570	C/T	--	--	--	--	--	--	0.10	0.050	0.152	0.741	201	No
	*CSMD1**	rs35051650	8	4859203	A/C	--	--	--	--	--	--	0.08	0.059	0.159	0.711	201	Yes
	PTPRO	rs7315300	12	15610293	A/T	--	--	--	--	--	--	0.26	-0.011	0.102	0.917	201	No
	*MCTP2**	rs12441824	15	94738631	A/G	0.32	0.005	0.006	0.438	38,238	No	0.41	0.053	0.084	0.526	201	No
	*TIAM1**	rs2833275	21	32489757	T/C	0.43	-0.000	0.004	0.933	38,238	Yes	0.34	-0.018	0.095	0.853	201	Yes
	*CTA-992D9.7**	rs4820743	22	27512801	T/C	--	--	--	--	--	--	0.39	0.003	0.092	0.974	201	Yes
HOMA -IR	*NFIA*	rs7535730	1	61871356	G/A	0.78	0.005	0.005	0.273	37,037	--	--	--	--	--	--	--
	RCOR1	rs12884198	14	103155465	A/G	0.04	0.014	0.011	0.189	37,037	--	--	--	--	--	--	--
	*MCTP2**	rs12441824	15	94738631	A/G	0.32	0.009	0.006	0.137	37,037	--	--	--	--	--	--	--

Abbreviations: SNP, single nucleotide polymorphism; CHR, chromosome; BP, base pair position (hg19 build); EA, effect allele; OA, other allele; EAF, effect allele frequency; *β*, beta coefficient; SE, standard error; *p*, p-value; Consist, consistent; FG, fasting glucose; FI, fasting insulin, HOMA-IR, homeostatic model of insulin resistance.

TABLE S6 Population Architecture using Genomics and Epidemiology (PAGE) Consortium validation results for rs77465890 and fasting insulin

		Not adjusted for BMI					Adjusted for BMI				
Ancestry group	**EA/OA**	***n***	**EAF**	***β***	**SE**	***p***	***n***	**EAF**	***β***	**SE**	***p***
African	C/T	7,696	0.02	-0.100	0.065	0.122	7,683	0.02	-0.113	0.067	0.092
Asian	C/T	1,900	0.14	0.007	0.046	0.885	1,898	0.14	0.027	0.048	0.574
European	C/T	18,656	0.03	0.044	0.054	0.417	18,637	0.03	0.015	0.054	0.787
Hispanic	C/T	14,301	0.07	-0.004	0.024	0.861	14,270	0.07	-0.015	0.024	0.535
Native Hawaiian	C/T	1,398	0.12	0.044	0.062	0.478	1,397	0.12	0.073	0.065	0.257
Overall[a]	C/T	44,349	0.06	-0.003	0.018	0.876	44,280	0.06	-0.006	0.018	0.758

[a]Additional ancestry groups with much smaller sample sizes are not shown individually but are included in the Overall group; thus, the Overall *N* exceeds the total of the shown subgroup sample sizes.

Abbreviations: EA, effect allele; OA, other allele; EAF, effect allele frequency; *β*, beta coefficient; SE, standard error; *p*, p-value.

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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

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9 | SUPPORTING INFORMATION

TABLE S1 Top independent signals in the Santiago Longitudinal Study for homeostatic model of insulin resistance

Gene/ Nearest gene*	SNP	CHR	BP	EA/OA	EAF	*β*	SE	*p*
GWAS-significant loci ($p<5x10^{-8}$)								
CSMD1	rs77465890	8	3628570	C/T	0.10	-0.322	0.057	1.66E-8
Suggestive loci ($p<5x10^{-6}$)								
*RP11-191N8.2**	rs35726538	1	221976039	G/A	0.02	0.693	0.142	1.16E-6
NFIA	rs7535730	1	61871356	G/A	0.18	0.236	0.049	1.50E-6
NCKAP5	rs528181067	2	134374835	A/T	0.01	-0.823	0.175	2.52E-6
*RP11-769N22.1**	rs184687999	4	29046057	C/T	0.05	0.415	0.087	1.86E-6
SPEF2	rs2361393	5	35800504	G/A	0.19	0.224	0.047	1.58E-6
*MCM9**	rs117381875	6	119134465	C/T	0.02	0.689	0.141	1.12E-6
*CSMD1**	rs35051650	8	4859203	A/C	0.13	0.269	0.055	9.49E-7
KIAA1217	rs143654218	10	24319915	G/A	0.01	0.968	0.206	2.54E-6
AKR1C3	rs117400599	10	5143717	G/T	0.04	0.467	0.097	1.55E-6
PTPRO	rs7315300	12	15610293	A/T	0.24	0.223	0.042	1.46E-7
RCOR1	rs12884198	14	103155465	A/G	0.02	0.831	0.157	1.23E-7
*MCTP2**	rs12441824	15	94738631	A/G	0.48	-0.240	0.046	1.69E-7
DCC	rs9950187	18	50636401	T/A	0.04	0.453	0.095	1.95E-6
*CTA-992D9.7**	rs4820743	22	27512801	T/C	0.78	0.207	0.044	2.26E-6

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

TABLE S2 Top independent signals in the Santiago Longitudinal Study for fasting glucose, fasting insulin, and homeostatic model assessment of insulin resistance, adjusted for CDC pediatric z-scores of body mass index.

Trait	Gene/ Nearest Gene*	SNP	CHR	BP	EA/OA	EAF	*β*	SE	*p*
FG	*RP11-147G16.1**	rs10157848	1	82996068	C/G	0.96	7.233	1.579	5.00E-6
	LOC101927665	rs6748653	2	200528810	T/A	0.21	3.023	0.643	2.60E-6
	*AC010149.4**	rs113214710	2	231442593	T/G	0.07	-5.069	1.100	4.03E-6
	*AC009223.2**	rs138154342	2	41452492	G/A	0.01	-14.391	2.975	1.31E-6
	TXNRD3	rs78870998	3	126352111	C/A	0.03	7.859	1.719	4.85E-6
	GBA3	rs79399931	4	22714327	A/C	0.02	-11.381	2.300	7.46E-7
	UCHL1-AS1	rs66475765	4	41230618	T/C	0.03	-8.210	1.770	3.53E-6
	CCSER1	rs79947031	4	91829969	C/T	0.11	4.108	0.882	3.22E-6
	*RP11-541P9.3**	rs189776108	5	162420388	T/C	0.05	5.905	1.284	4.26E-6
	ZBED3-AS1	rs28589776	5	76406470	T/C	0.01	-11.552	2.492	3.56E-6
	DCBLD1	rs117533208	6	117855911	C/T	0.02	10.528	2.291	4.32E-6
	MAN1A1	rs62418805	6	119508342	C/T	0.32	3.055	0.604	4.19E-7
	*AC004535.2**	rs141226872	7	10748548	G/A	0.01	12.046	2.622	4.34E-6
	*RPL7**	rs12546395	8	74194405	A/T	0.62	-2.573	0.533	1.40E-6
	SLC24A2	rs79818403	9	19669933	T/C	0.01	15.296	3.100	8.06E-7
	WNK2	rs147515244	9	96046087	A/T	0.05	6.730	1.389	1.26E-6
	*RP11-432B10.1**	rs7476984	10	109170924	A/G	0.40	2.825	0.540	1.72E-7
	*AL157931.1**	rs117292932	13	23574827	A/T	0.02	9.998	2.067	1.31E-6
	RTN4RL1	rs11656601	17	1924911	T/C	0.25	-3.534	0.732	1.36E-6
	ATP9B	rs7226934	18	76904665	C/T	0.16	3.377	0.730	3.74E-6
	*NLRP12**	rs139295665	19	54336151	A/G	0.01	-17.044	3.620	2.50E-6
	*RP11-560A15.4**	rs6092424	20	55672544	A/G	0.49	-2.667	0.534	5.82E-7
	*TAF4**	rs6061420	20	60654074	G/A	0.07	-6.021	1.274	2.29E-6
	*RP5-839B4.8**	rs80352176	20	9952118	G/A	0.09	-4.994	1.038	1.52E-6
	*PARVG**	rs139198	22	44606772	C/T	0.22	3.040	0.662	4.47E-6
FI	*ENSA**	rs115406107	1	150594155	A/T	0.02	0.508	0.105	1.00E-6
	KAZN	rs80204739	1	15065485	G/C	0.02	0.580	0.127	5.00E-6
	*PLD5**	rs61839743	1	242873445	C/T	0.01	-0.883	0.185	2.00E-6
	SMEK2	rs60356354	2	55833911	C/T	0.03	-0.452	0.095	2.06E-6
	LINC00290	rs6831952	4	182066235	T/G	0.67	0.164	0.035	3.04E-6
	*RP11-434D11.4**	rs1546499	5	126033156	C/A	0.43	0.146	0.031	2.13E-6
	SPEF2	rs2361394	5	35800547	G/A	0.08	0.287	0.056	2.80E-7
	*RP11-744I24.2**	rs7795885	7	141251044	G/C	0.03	0.427	0.093	4.20E-6
	DOCK5	rs2709613	8	25212994	C/G	0.97	0.474	0.101	3.03E-6
	CSMD1	rs77465890	8	3628570	C/T	0.10	-0.252	0.047	1.03E-7
	*CSMD1**	rs34371265	8	4859170	C/T	0.13	0.216	0.045	1.82E-6
	*PRAG1**	rs577483743	8	8376874	A/T	0.02	-0.516	0.111	3.61E-6
	*AL157884.1**	rs12337921	9	32735066	A/G	0.02	-0.550	0.117	2.61E-6
	*CTD-2507G9.1**	rs11029253	11	26163242	A/T	0.09	0.268	0.058	3.04E-6
	RCOR1	rs12884198	14	103155465	A/G	0.02	0.663	0.130	3.28E-7
	MAP4K5	rs77026144	14	50937785	T/C	0.01	0.942	0.187	4.80E-7
	CIITA	rs45513895	16	10995145	C/T	0.03	-0.419	0.088	2.12E-6
	APBA3	rs10460192	19	3756197	C/T	0.77	0.172	0.037	4.24E-6
	PLXNB2	rs62241209	22	50734392	A/G	0.15	0.213	0.045	2.59E-6
HOMA-IR	*ENSA**	rs115406107	1	150594155	A/T	0.02	0.537	0.114	2.00E-6
	KAZN	rs80204739	1	15065485	G/C	0.02	0.643	0.137	3.00E-6
	NFIA	rs2499526	1	61870696	T/C	0.55	-0.150	0.033	4.00E-6
	*RP11-434D11.4**	rs1546499	5	126033156	C/A	0.43	0.153	0.033	4.02E-6
	SPEF2	rs2361394	5	35800547	G/A	0.08	0.305	0.060	4.52E-7
	*MCM9**	rs117381875	6	119134465	C/T	0.02	0.594	0.126	2.48E-6
	CSMD1	rs77465890	8	3628570	C/T	0.10	-0.275	0.051	7.11E-8
	*CSMD1**	rs34371265	8	4859170	C/T	0.13	0.237	0.049	1.21E-6
	*PRAG1**	rs577483743	8	8376874	A/T	0.02	-0.554	0.120	4.09E-6
	*CTD-2507G9.1**	rs1489506	11	26126773	A/C	0.10	0.258	0.056	4.73E-6
	RCOR1	rs12884198	14	103155465	A/G	0.02	0.692	0.140	8.41E-7
	MAP4K5	rs77026144	14	50937785	T/C	0.01	1.054	0.202	1.75E-7
	*RP11-66B24.5**	rs149208997	15	101334196	T/C	0.01	-0.931	0.200	3.44E-6
	DNAH17	rs1530433	17	76559768	C/T	0.56	-0.161	0.033	1.44E-6
	APBA3	rs10460192	19	3756197	C/T	0.77	0.193	0.040	1.59E-6
	PLXNB2	rs62241209	22	50734392	A/G	0.15	0.228	0.049	3.08E-6

Abbreviations: SNP, single nucleotide polymorphism; CHR, chromosome; BP, base pair position (hg19 build); EA, effect allele; OA, other allele; EAF, effect allele frequency; *β*, beta coefficient; SE, standard error; *p*, p-value; FG, fasting glucose; FI, fasting insulin; HOMA-IR, homeostatic model assessment of insulin resistance.

TABLE S3 Loci reported in other studies to have GWAS-significant associations with fasting glucose that did not generalize in the Santiago Longitudinal Study. Associations either did not reach the nominal significance threshold of $p<0.05$ or showed a direction of effect inconsistent with other studies. p-values for nominally significant associations are bolded.

Gene/ nearest gene*	SNP	PMID	CHR	BP	EA/ OA	EAF	β	SE	p	Direction of effect consistent with other studies?
	rs79687284	28270201 [1]	1	214150821	C/G	0.02	3.430	2.503	0.171	Yes
PROX1-AS1	rs340874	20081858 [2], 22581228 [3]	1	214159256	C/T	0.39	-0.350	0.579	0.545	No
*Metazoa_SRP**	rs17407594	25223902 [4]	1	66170362	A/G	0.19	0.442	0.798	0.541	Yes
	rs477224	28905132 [5]	2	169750483	T/C	0.73	-0.550	0.627	0.381	Different alleles (EA/OA:A/G) reported in other study.
*SPC25**	rs13387347	25187374 [6]	2	169754846	C/T	0.38	-1.346	0.555	**0.015**	No
*AC018712.3**	rs733331	25187374 [6]	2	173546313	A/G	0.13	-0.580	0.804	0.470	No
DPYSL5	rs1371614	22581228 [3]	2	27152874	T/C	0.38	-0.250	0.546	0.647	No
	rs780095	28270201 [1]	2	27741105	G/A	0.64	0.226	0.564	0.689	Yes
GCKR	rs780094	20081858 [2], 22581228 [3], 25187374 [6]	2	27741237	C/T	0.67	-0.091	0.574	0.874	Other studies inconsistent with one another.
MRPL33	rs3736594	22581228 [3]	2	27995781	C/A	0.60	0.154	0.544	0.777	No
*AC012354.6**	rs895636	25187374 [6]	2	45188353	T/C	0.27	-0.703	0.614	0.252	No
ADCY5	rs11708067	20081858 [2], 22581228 [3]	3	123065778	G/A	0.28	-0.410	0.582	0.482	Yes
	rs11920090	20081858 [2], 22581228 [3]	3	170717521	A/T	0.11	-0.332	0.886	0.708	Other studies inconsistent with one another.
	rs8192675	28270201 [1]	3	170724883	C/T	0.34	-0.191	0.575	0.740	No
SLC2A2	rs9873618	28270201 [1]	3	170733076	A/G	0.33	-0.342	0.577	0.554	No
IGF2BP2	rs7651090	22885924 [7]	3	185513392	G/A	0.32	0.025	0.578	0.965	Yes
AMT	rs11715915	22885924 [7]	3	49455330	T/C	0.16	-0.508	0.730	0.486	Yes
ZBED3-AS1	rs7708285	22885924 [7]	5	76425867	A/G	0.69	-0.850	0.594	0.152	Yes
	rs4869272	22885924 [7]	5	95539448	T/C	0.81	1.195	0.702	0.089	Yes
LOC101929710	rs13179048	22581228 [3]	5	95542726	A/C	0.18	-1.427	0.714	**0.046**	No
CDKAL1	rs9356744	25187374 [6]	6	20685486	C/T	0.27	-0.235	0.596	0.694	No
	rs17762454	22885924 [7]	6	7213200	T/C	0.40	0.109	0.569	0.849	Yes
RREB1	rs35742417	25625282 [8]	6	7247344	A/C	0.06	-0.723	1.148	0.529	Yes
	rs2191349	20081858 [2], 22581228 [3]	7	15064309	T/G	0.39	0.581	0.559	0.298	Yes
*AC006458.3**	rs1974620	25187374 [6]	7	15065467	T/C	0.39	0.578	0.559	0.301	Yes
	rs10259649	26132169 [9]	7	44219705	C/T	0.24	0.597	0.632	0.345	Yes
GCK	rs730497	25187374 [6]	7	44223721	A/G	0.18	0.506	0.698	0.469	Yes
	rs1799884	23575436 [10]	7	44229068	T/C	0.18	0.446	0.697	0.523	Different effect allele (EA:A) reported in other study.
*GCK**	rs4607517	19060907 [11], 20081858 [2], 22581228 [3]	7	44235668	A/G	0.18	0.428	0.699	0.540	Yes
YKT6	rs917793	28270201 [1]	7	44245853	T/A	0.29	-0.070	0.602	0.908	No
*CAMK2B**	rs878521	26132169 [9]	7	44255643	A/G	0.33	0.264	0.574	0.645	Yes
	rs10248619	22581228 [3]	7	50751090	C/T	0.78	-0.514	0.641	0.422	Yes
GRB10	rs6943153	22885924 [7]	7	50791579	C/T	0.56	-0.765	0.560	0.172	Yes
	rs13266634	28270201 [1]	8	118184783	T/C	0.21	-1.069	0.637	0.094	No
	rs3802177	25187374 [6]	8	118185025	A/G	0.21	-1.097	0.637	0.085	Yes
SLC30A8	rs11558471	20081858 [2], 21873549 [12], 22581228 [3], 28270201 [1]	8	118185733	G/A	0.22	-1.165	0.623	0.062	Other studies inconsistent with one another.
*RP11-115J16.1**	rs983309	22885924 [7]	8	9177732	G/T	0.78	-0.682	0.634	0.282	Yes
LOC157273	rs4841132	22581228 [3]	8	9183596	G/A	0.79	-0.459	0.662	0.488	Yes
*ABO**	rs651007	25631608 [13]	9	136153875	T/C	0.15	0.494	0.748	0.509	Different alleles (EA/OA:A/G) reported in other study.
DNLZ	rs3829109	22885924 [7]	9	139256766	A/G	0.43	-1.006	0.541	0.063	Yes
*CDKN2B-AS1**	rs10811661	25187374 [6]	9	22134094	C/T	0.14	0.468	0.780	0.548	No
	rs7034200	20081858 [2]	9	4289050	A/C	0.53	0.768	0.573	0.180	Yes
GLIS3	rs4237150	25187374 [6]	9	4290085	C/G	0.47	0.783	0.569	0.169	Yes
KANK1	rs10815355	25187374 [6]	9	622523	T/G	0.06	-0.149	1.167	0.898	No
*RP11-381K7.1**	rs10885122	20081858 [2]	10	113042093	G/T	0.86	-0.378	0.798	0.636	No
	rs4506565	20081858 [2]	10	114756041	T/A	0.24	-0.431	0.662	0.515	No
	rs7903146	21873549 [12]	10	114758349	T/C	0.24	-0.227	0.664	0.733	No
TCF7L2	rs12243326	22581228 [3]	10	114788815	C/T	0.21	-0.035	0.678	0.959	Yes

CRY2	rs11605924	20081858 [2], 22581228 [3]	11	45873091	C/A	0.57	-0.122	0.526	0.817	Yes
MADD	rs7944584	20081858 [2], 22581228 [3]	11	47336320	T/A	0.19	0.672	0.676	0.320	No
*OR4S1**	rs1483121	22581228 [3]	11	48333360	A/G	0.08	0.139	1.000	0.890	Yes
FADS1	rs174550	20081858 [2], 22581228 [3]	11	61571478	C/T	0.62	0.060	0.566	0.915	No
ARAP1	rs11603334	22581228 [3]	11	72432985	A/G	0.07	-1.506	1.078	0.162	No
	rs3847554	25187374 [6]	11	92668826	T/C	0.29	0.590	0.597	0.322	Yes
	rs1387153	19060909 [14]	11	92673828	T/C	0.21	1.251	0.664	0.059	Yes
	rs7936247	23903356 [15]	11	92690032	T/G	0.24	1.054	0.622	0.090	Yes
	rs2166706	19651812 [16]	11	92691532	C/T	0.27	1.046	0.610	0.086	Different alleles (EA/OA:G/A) reported in other study.
*RP11-676F20.1**	rs10830962	23575436 [10]	11	92698427	G/C	0.29	0.806	0.598	0.178	No
*RP11-503G7.2**	rs10747083	22885924 [7]	12	133041618	A/G	0.72	-0.163	0.588	0.782	No
GLS2	rs2657879	22885924 [7]	12	56865338	G/A	0.22	0.501	0.642	0.435	Yes
RMST	rs17331697	26132169 [9]	12	97868906	C/T	0.04	-0.365	1.291	0.777	Yes
*PDX1-AS1**	rs2293941	22581228 [3]	13	28491198	A/G	0.33	1.071	0.578	0.064	Yes
PDX1	rs7981781	28270201 [1]	13	28499962	A/G	0.33	1.136	0.610	0.063	Yes
WARS	rs3783347	22885924 [7]	14	100839261	T/G	0.11	-0.566	0.861	0.511	Yes
*C2CD4A**	rs7173964	22581228 [3]	15	62396942	A/G	0.48	-0.073	0.538	0.892	No
IGF1R	rs2018860	25187374 [6]	15	99258710	T/A	0.54	-0.528	0.548	0.336	Yes
QPCTL	rs2302593	22885924 [7]	19	46196634	G/C	0.52	0.693	0.545	0.204	No
LINC00261	rs6113722	22885924 [7]	20	22557099	A/G	0.04	1.144	1.444	0.428	No
*LINC00261**	rs6048205	22581228 [3]	20	22559601	G/A	0.04	0.269	1.374	0.845	No
*RP4-788L20.3**	rs1209523	20152958 [17]	20	22567942	T/C	0.03	1.741	1.577	0.269	No
LOC101929685	rs6048216	25187374 [6]	20	22581268	C/T	0.04	1.265	1.371	0.356	No
TOP1	rs6072275	22885924 [7]	20	39743905	A/G	0.14	0.753	0.805	0.349	Yes

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

TABLE S4 Loci reported in other studies to have GWAS-significant associations with fasting insulin that did not generalize in the Santiago Longitudinal Study. No associations reached the nominal significance threshold of $p<0.05$ for this trait.

Gene/ nearest gene*	SNP	PMID	CHR	BP	EA/ OA	EAF	*β*	SE	*p*	Direction of effect consistent with other studies?
*RP11-95P13.1**	rs2820436	22885924 [7]	1	219640680	C/A	0.51	0.044	0.034	0.193	Yes
	rs2785980	22581228 [3]	1	219700519	C/T	0.54	-0.009	0.036	0.794	Yes
*RP11-95P13.2**	rs4846565	22885924 [7]	1	219722104	A/G	0.54	0.018	0.035	0.612	No
MAP3K19	rs1530559	22885924 [7]	2	135755629	G/A	0.68	0.005	0.042	0.911	No
LOC101929615	rs10195252	22885924 [7]	2	165513091	C/T	0.22	0.024	0.044	0.592	No
COBLL1	rs7607980	22581228 [3]	2	165551201	C/T	0.07	-0.008	0.068	0.910	Yes
	rs2943634	22581228 [3]	2	227068080	C/A	0.83	0.022	0.047	0.643	No
*AC068138.1**	rs2943645	22885924 [7]	2	227099180	T/C	0.82	0.038	0.045	0.399	Yes
GCKR	rs780094	20081858 [2], 22581228 [3]	2	27741237	C/T	0.67	0.062	0.036	0.089	Other studies inconsistent with one another.
*AY269186.2**	rs9841287	22581228 [3]	3	108993	G/A	0.34	-0.034	0.036	0.338	Yes
PPARG	rs17036328	22885924 [7]	3	12390484	C/T	0.12	-0.016	0.054	0.775	Yes
	rs974801	22885924 [7]	4	106071064	G/A	0.38	0.001	0.036	0.970	Yes
TET2	rs9884482	22885924 [7]	4	106081636	C/T	0.38	-0.006	0.036	0.866	No
	rs4691380	22581228 [3]	4	157720124	T/C	0.35	0.038	0.035	0.283	Yes
PDGFC	rs6822892	22885924 [7]	4	157734675	G/A	0.35	0.041	0.035	0.244	No
MSMO1	rs17046216	22791750 [18]	4	166255704	A/T	0.21	0.049	0.044	0.264	Yes
FAM13A	rs3822072	22885924 [7]	4	89741269	A/G	0.38	0.008	0.036	0.823	Yes
ARL15	rs4865796	22885924 [7]	5	53272664	A/G	0.84	-0.023	0.049	0.645	No
*AC022431.2**	rs459193	22885924 [7]	5	55806751	G/A	0.79	0.042	0.042	0.320	Yes
RSPO3	rs2745353	22885924 [7]	6	127452935	T/C	0.61	-0.009	0.036	0.802	No
UHRF1BP1	rs6912327	22885924 [7]	6	34764922	C/T	0.24	0.059	0.039	0.131	No
*UHRF1BP1**	rs4646949	22581228 [3]	6	34845449	G/T	0.38	0.033	0.035	0.337	No
HIP1	rs1167800	22885924 [7]	7	75176196	A/G	0.61	-0.006	0.037	0.880	No
*RP11-115J16.1**	rs983309	22885924 [7]	8	9177732	G/T	0.78	-0.059	0.040	0.141	Yes
	rs4841132	22581228 [3]	8	9183596	G/A	0.79	-0.066	0.042	0.115	Yes
LOC157273	rs2126259	22885924 [7]	8	9185146	C/T	0.73	-0.031	0.039	0.419	Yes
TCF7L2	rs7903146	22581228, [3] 22885924 [7]	10	114758349	T/C	0.24	-0.016	0.042	0.701	Other studies inconsistent with one another.
*MIR378C**	rs7077836	22791750 [18]	10	132751498	A/G	0.11	0.007	0.055	0.896	Different effect allele (EA:T) reported in other study.
IGF1	rs35767	20081858 [2]	12	102875569	G/A	0.84	0.038	0.049	0.433	Yes
*IGF1**	rs35747	22581228 [3]	12	102912558	A/G	0.83	0.035	0.048	0.463	Yes
FTO	rs1421085	22885924 [7]	16	53800954	C/T	0.23	0.063	0.041	0.122	Yes
PEPD	rs731839	22885924 [7]	19	33899065	A/G	0.65	0.035	0.036	0.322	No

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

TABLE S5 Meta-Analyses of Glucose and Insulin-Related Traits Consortium (MAGIC) and Nonalcoholic Steatohepatitis (NASH) validation results for top independent fasting glucose, fasting insulin, and homeostatic model of insulin resistance results. Variants with minor allele count <10 in these studies not shown.

						MAGIC						NASH					
	Gene/ Nearest gene*	SNP	CHR	BP	EA/ OA	EAF	*β*	SE	*p*	*n*	Consist. direction of effect?	EAF	*β*	SE	*p*	*n*	Consist. direction of effect?
FG	*LOC101927665*	rs6748653	2	200528810	T/A	--	--	--	--	--	--	0.12	1.616	1.393	0.247	207	Yes
	*AC010149.4**	rs113214710	2	231442593	T/G	--	--	--	--	--	--	0.05	0.983	1.969	0.618	207	No
	CCSER1	rs79947031	4	91829969	C/T	--	--	--	--	--	--	0.13	0.802	1.270	0.529	207	Yes
	MAN1A1	rs62418805	6	119508342	C/T	--	--	--	--	--	--	0.28	-0.066	1.079	0.951	207	No
	*RPL7**	rs12546395	8	74194405	A/T	--	--	--	--	--	--	0.68	0.212	0.981	0.829	207	No
	*RP11-432B10.1**	rs7476984	10	109170924	A/G	--	--	--	--	--	--	0.38	0.355	0.927	0.702	207	Yes
	RTN4RL1	rs11656601	17	1924911	T/C	--	--	--	--	--	--	0.23	0.253	1.103	0.819	207	No
	ATP9B	rs7226934	18	76904665	C/T	--	--	--	--	--	--	0.19	1.847	1.145	0.108	207	Yes
	*RP5-839B4.8**	rs80352176	20	9952118	G/A	--	--	--	--	--	--	0.12	-0.486	1.362	0.722	207	Yes
	*RP11-560A15.4**	rs6092424	20	55672544	A/G	--	--	--	--	--	--	0.41	-0.180	0.878	0.837	207	Yes
	*PARVG**	rs139198	22	44606772	C/T	--	--	--	--	--	--	0.20	-0.073	1.117	0.948	207	No
FI	*NFIA*	rs7535730	1	61871356	G/A	0.78	0.003	0.005	0.501	38,238	Yes	0.18	0.005	0.112	0.967	201	Yes
	IQCB1	rs2331964	3	121542898	C/T	0.66	-0.004	0.004	0.295	38,238	No	0.26	0.016	0.098	0.871	201	Yes
	SPEF2	rs2361394	5	35800547	G/A	0.94	-0.003	0.009	0.768	38,238	No	0.07	-0.166	0.164	0.312	201	No
	CSMD1	rs77465890	8	3628570	C/T	--	--	--	--	--	--	0.10	0.050	0.152	0.741	201	No
	*CSMD1**	rs35051650	8	4859203	A/C	--	--	--	--	--	--	0.08	0.059	0.159	0.711	201	Yes
	PTPRO	rs7315300	12	15610293	A/T	--	--	--	--	--	--	0.26	-0.011	0.102	0.917	201	No
	*MCTP2**	rs12441824	15	94738631	A/G	0.32	0.005	0.006	0.438	38,238	No	0.41	0.053	0.084	0.526	201	No
	*TIAM1**	rs2833275	21	32489757	T/C	0.43	-0.000	0.004	0.933	38,238	Yes	0.34	-0.018	0.095	0.853	201	Yes
	*CTA-992D9.7**	rs4820743	22	27512801	T/C	--	--	--	--	--	--	0.39	0.003	0.092	0.974	201	Yes
HOMA -IR	*NFIA*	rs7535730	1	61871356	G/A	0.78	0.005	0.005	0.273	37,037	--	--	--	--	--	--	--
	RCOR1	rs12884198	14	103155465	A/G	0.04	0.014	0.011	0.189	37,037	--	--	--	--	--	--	--
	*MCTP2**	rs12441824	15	94738631	A/G	0.32	0.009	0.006	0.137	37,037	--	--	--	--	--	--	--

Abbreviations: SNP, single nucleotide polymorphism; CHR, chromosome; BP, base pair position (hg19 build); EA, effect allele; OA, other allele; EAF, effect allele frequency; *β*, beta coefficient; SE, standard error; *p*, p-value; Consist, consistent; FG, fasting glucose; FI, fasting insulin, HOMA-IR, homeostatic model of insulin resistance.

TABLE S6 Population Architecture using Genomics and Epidemiology (PAGE) Consortium validation results for rs77465890 and fasting insulin

		Not adjusted for BMI					Adjusted for BMI				
Ancestry group	**EA/OA**	***n***	**EAF**	***β***	**SE**	***p***	***n***	**EAF**	***β***	**SE**	***p***
African	C/T	7,696	0.02	-0.100	0.065	0.122	7,683	0.02	-0.113	0.067	0.092
Asian	C/T	1,900	0.14	0.007	0.046	0.885	1,898	0.14	0.027	0.048	0.574
European	C/T	18,656	0.03	0.044	0.054	0.417	18,637	0.03	0.015	0.054	0.787
Hispanic	C/T	14,301	0.07	-0.004	0.024	0.861	14,270	0.07	-0.015	0.024	0.535
Native Hawaiian	C/T	1,398	0.12	0.044	0.062	0.478	1,397	0.12	0.073	0.065	0.257
Overall[a]	C/T	44,349	0.06	-0.003	0.018	0.876	44,280	0.06	-0.006	0.018	0.758

[a]Additional ancestry groups with much smaller sample sizes are not shown individually but are included in the Overall group; thus, the Overall *N* exceeds the total of the shown subgroup sample sizes.
Abbreviations: EA, effect allele; OA, other allele; EAF, effect allele frequency; *β*, beta coefficient; SE, standard error; *p*, p-value.

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