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Clinical Research Article

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Genome-wide Association Study of Lipid Traits in Youth With Type 2 Diabetes

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Abstract

Context: Dyslipidemia is highly prevalent in youth with type 2 diabetes (T2D), yet the pathogenic components of dyslipidemia in youth with T2D are poorly understood.
Objective: To evaluate the genetic determinants of lipid traits in youth with T2D through a genome-wide association study.
Design, Participants, and Main Outcome Measures: We genotyped 206 928 variants and imputed 17 642 824 variants in 1076 youth (mean age 15.0 ± 2.48 years) with T2D from the Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) and SEARCH for Diabetes in Youth (SEARCH) studies as part of the Progress in Diabetes Genetics in Youth (ProDiGY) consortium. We performed association testing for triglyceride and low-density lipoprotein cholesterol and high-density lipoprotein cholesterol (HDL-c) concentrations adjusted for the genetic relationship matrix within each substudy followed by meta-analyses for each trait.

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Results: We identified a novel association between a deletion on chromosome 3 (3:67817380_AT/A_Deletion:RP11-81N13.1) and triglyceride levels at genome-wide level of significance ($P = 2.3 \times 10^{-8}$) with each risk allele increasing triglycerides by 20%. We also identified a genome-wide significant signal at rs247617 ($P = 5.1 \times 10^{-9}$) between *HERFUD1* and *CETP* associated with HDL-c, with carriers of 1 copy of the risk allele having twice higher HDL-c.

Conclusions: Our genetic analyses of lipid traits in youth with T2D have identified 1 novel and 1 previously known locus. Additional studies are needed to further characterize the genetic architecture of dyslipidemia in youth with T2D.

Key Words: type 2 diabetes, youth, dyslipidemia, genetics, triglycerides, LDL-c, HDL-c

Over the last 2 decades, type 2 diabetes (T2D) in youth has emerged as a complication of early-onset obesity, affecting about 0.46 per 1000 youth [1]. Pediatric T2D usually manifests during puberty when puberty-related insulin resistance exacerbates obesity-related insulin resistance [2]. Dyslipidemia, which is both a comorbidity and a complication, is highly prevalent in youth with T2D [3]. However, the pathogenic components of dyslipidemia in youth with T2D are poorly understood. Similar to adults, glycemic control and duration of T2D are key contributors to dyslipidemia in youth [3]. Interestingly, not all youth with T2D develop dyslipidemia, even if obese.

The Treatment Options for Type 2 Diabetes in Adolescents and Youth (TODAY) study showed that elevated plasma concentrations of triglycerides ≥ 150 mg/dL were present in 21% of participants, low-density lipoprotein cholesterol (LDL-c) plasma concentrations ≥ 130 mg/dL were present in 4.5% of participants and high-density lipoprotein cholesterol (HDL-c) plasma concentrations ≤50 mg/dL in males and 40 mg/dL in females were present in 80% participants with newly diagnosed T2D at study enrollment [4]. Similarly, data from SEARCH for Diabetes in Youth (SEARCH) in 2001 and 2002 showed the high prevalence of dyslipidemia in youth with T2D with 24% with triglyceride levels ≥ 150 mg/dL, 15% with LDL-c levels ≥ 130 mg/dL, and 24% with total cholesterols levels ≥ 200 mg/dL [5].

Lipid traits including plasma levels of cholesterol, triglycerides, and lipoproteins are complex traits, whose variation is estimated to be determined by the interplay of genetic and environmental factors [6]. Previous genome-wide association studies (GWAS) in large populations of adults have discovered greater than 150 genetic variants associated with lipid traits [7]. These adult studies have also included small cohorts of children, but, to date, the contribution of genetic variants to dyslipidemia in youth with T2D remains unknown. The objective of this study is to discover the genetic determinants of lipids traits specifically in the context of T2D. To uncover the genetic underpinnings of dyslipidemia in youth with T2D, we performed a GWAS of lipid traits in a group of 1076 obese youth with T2D in the Progress in Diabetes Genetics in Youth (ProDiGY) consortium, composed of participants originally enrolled in 2 different pediatric studies: the TODAY study [8] and the SEARCH study [9].

Materials and Methods

Description of Participants

ProDiGY includes data from over 3000 cases with youth-onset T2D and 6000 diabetes-free adult controls. The cohort with diabetes includes 449 youth from the TODAY study, over 2000 youth with T2D from the TODAY ancillary genetics study, and 468 youth with T2D from SEARCH. The study also accesses data from over 10 000 adult cases and 10 000 controls from T2D-GENES [10]. This analysis included the subset of cases with lipid data, collected when the participants were enrolled: 539 participants from TODAY and 537 participants from SEARCH.

The TODAY and SEARCH studies are described in detail elsewhere [11,12]. TODAY and SEARCH protocols were approved by the institutional review boards of each participating institution. Participants provided written informed parental consent and child assent, including consent and assent specifically for genetic testing.

Lipid Measurements

In both TODAY and SEARCH studies, lipid analyses were performed in the same central laboratory using Roche reagents on a Roche Modular P autoanalyzer (Roche Diagnostics, Indianapolis, IN, USA) with methods standardized to the Centers for Disease Control and Prevention Reference Methods [13]. HDL-c was measured after precipitation of apolipoprotein B–containing particles with dextran sulfate Mg2+. LDL-c was calculated using the

Friedewald equation [14], except if plasma triglyceride concentrations were >400 mg/dL, in which case lipoprotein analyses were performed after ultracentrifugation using the Lipid Research Clinic Beta Quantification procedure. The TODAY study protocol defined lipid goals as LDL-c < 100mg/dL and triglycerides < 150 mg/dL. If lipid levels were outside the target range, initial therapy consisted of dietary counseling. If LDL-c remained ≥130 mg/dL or if triglyceride values remained 300–599 mg/dL after 6 months of dietary counseling and diabetes management, pharmacological treatment with atorvastatin was initiated. If triglycerides were ≥600 mg/dL, fibrate therapy could be initiated at the discretion of the treating physician [11]. Participants in SEARCH had lipid management based on the discretion of their treating physician. Participants on lipid-lowering medications were not removed from these analyses.

Genotyping, Imputation, and Quality Control

ProDiGY samples were genotyped on the Infinium array by the Genetic Analysis Platform at the Broad Institute. The directly genotyped data were called by using the Autocall algorithm. All quality control steps were run in PLINK2 and R-3.4. Imputation was done using the Michigan Imputation Server against the 1000G Phase 3 v5 panel as the reference. After cleaning, 17 642 824 single nucleotide polymorphisms remained.

Statistical Analysis

Baseline lipid traits including LDL-c, HDL-c, and triglycerides were analyzed with a generalized linear mixed model (EMMAX) by using the Efficient and Parallelizable Association Container Toolbox (EPACTS) within the TODAY and SEARCH cohorts. Meta-analyses were run by METAL to combine the results from each cohort. A threshold of $P < 5 \times 10^{-8}$ was used to define genome-wide significance.

Results

The clinical characteristics of the study populations at baseline are shown in Table 1. Mean age of the participants with T2D was 15.0 ± 2.48 years, 62.6% were female, mean body mass index *z*-score was 2.17 ± 0.57, and mean hemoglobin A1c was 6.73 ± 1.84%. We discovered genome-wide significant signals for HDL-c and triglycerides. The GWAS for HDL-c showed a genome-wide significant association at rs247617 in chromosome 16 ($P = 5.1 \times 10^{-9}$) (Fig. 1). rs247617 represents a cytosine-to-adenine change in a regulatory region (CTCF binding site) of chromosome 16 in close proximity to the *CETP* gene. The minor allele frequencies of rs247617 in each ethnicity and study are shown in Table 2. Characteristics of the study group according to the rs247617 genotypes are shown in Table 3. Participants carrying 1 copy of the minor rs247617 allele had 1.1 times higher HDL-c plasma levels as compared to participants homozygous for the common allele ($P = 0.01$). We also discovered a genome-wide significant association for triglycerides at rs148323096 ($P = 2.3 \times 10^{-8}$) on chromosome 3 characterized by a deletion of 1 T (ancestral TT) in the last intron of the *SUCLG2-AS1* gene. Frequency of the T deletion in each study by ethnicity is shown in Table 4. rs148323096 was associated with triglycerides in both TODAY ($P = 0.03$) and SEARCH ($P = 0.03$) studies. Characteristics of the study group according to the rs148323096 genotypes are shown in Table 5. Participants with deletion of 1 T allele had 2.19 times ($P = 2.26 \times 10^{-8}$) higher triglyceride levels compared to participants without the deletion. The GWAS for LDL-c did not reveal any genome-wide significant associations.

Table 1. Clinical characteristics of the study groups

	TODAY (n = 539)	SEARCH (n = 498)	Total (n = 1037)
Age (years)	14.4 ± 2.01	15.6 ± 2.80	15.0 ± 2.48
Sex (girls), %	64.0	60.9	62.6
BMI *z*-score	2.22 ± 0.47	2.12 ± 0.66	2.17 ± 0.57
Lipid traits			
TRIG (mg/dL)	115.6 ± 80.71	159.1 ± 170.2	136.6 ± 133.2
LDL-c (mg/dL)	83.9 ± 24.4	105.4 ± 31.82	94.2 ± 30.2
HDL-c (mg/dL)	38.7 ± 8.59	41.2 ± 10.4	39.9 ± 9.5
Lipid medication, %	1[a]	2.6	1.7
Glycemic parameters			
Glucose (mg/dL)	110.4 ± 23.8	156.4 ± 82.2	132.4 ± 63.6
Insulin (uU/mL)	30.9 ± 22.3	32.5 ± 34.1	31.4 ± 26.2
HbA1c, %	6.01 ± 0.75	7.53 ± 2.32	6.73 ± 1.84
T2D duration (years)	0.7 ± 0.5	1.5 ± 1.5	1.1 ± 1.2

The table shows the baseline clinical characteristics of the participants enrolled in SEARCH and TODAY separately and combined. Data are shown as mean and SD.

Abbreviations: BMI, body mass index; HbA1c, hemoglobin A1c; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; SEARCH, SEARCH for Diabetes in Youth; T2D, type 2 diabetes mellitus; TODAY, Treatment Options for Type 2 Diabetes in Adolescents and Youth; TRIG, triglycerides.

[a]At randomization.

Discussion

To our knowledge, this is the first GWAS of lipid traits performed in a cohort of youth with T2D. Despite the relatively small sample size for a GWAS, we were able to replicate

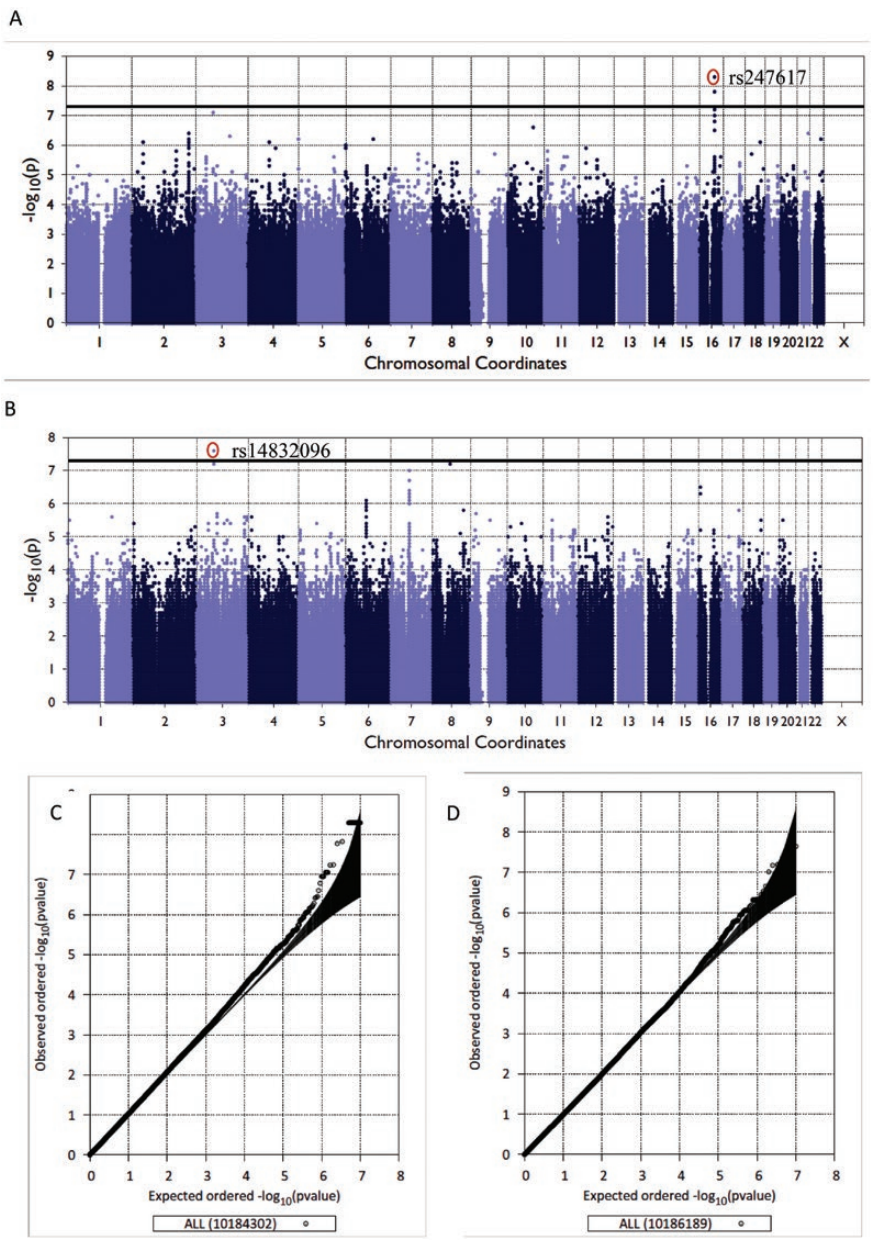

Figure 1. This figure shows the Manhattan plot for the association with high-density lipoprotein cholesterol (HDL-C) (A) and triglycerides (B). (C) and (D) show the Q-Q plots for HDL-c and triglycerides, respectively.

a previously discovered association between rs247617 in *CETP* and HDL-c and discover a new association between rs148323096 near the *SUCLG2-AS1* gene and plasma triglyceride concentrations. The contributions of adiposity, insulin resistance, and dysglycemia are difficult to disentangle in the pathogenesis of dyslipidemia in T2D. Our results shed light on the genetic contribution of dyslipidemia specifically in the context of T2D while still accounting for the role of dysglycemia and adiposity.

Participants carrying 1 copy of the minor rs247617 allele had higher plasma HDL-c levels as compared to participants homozygous for the common allele. This observation is consistent with observations in larger studies in adults [15,16]. The *CETP* gene product is the cholesteryl ester transfer protein, whose function is to transfer cholesteryl esters from HDL-c to apolipoprotein B–containing particles [17]. rs247617 in the *CETP* gene is characterized by a cytosine-to-adenine substitution in the regulatory region of the *CETP* gene and the presence of the minor allele is predicted to reduce the expression of the *CETP* gene causing a rise in HDL-c levels [18]. This variant has been associated with lower concentrations of triglycerides in very low-density lipoprotein, intermediate low-density lipoprotein, and HDL-c [19]. Additionally, observational data in 3 adult population-based cohorts totaling 616 incident cases and 13 564 controls during 8 years of follow-up showed that genetic variation in *CETP* was associated with reduced cardiovascular disease risk [19]. Overall, data from adults

Table 2. Minor allele frequencies and Hardy-Weinberg equilibrium of rs247617 genotype in *CEPT* gene by ancestral group

	TODAY			SEARCH			Total		
	C/C	A/C	A/A	C/C	A/C	A/A	C/C	A/C	A/A
n	287	214	38	253	200	45	540	414	83
MAF									
EUR		0.27			0.31			0.29	
AFR		0.28			0.28			0.28	
AMR		0.27			0.30			0.29	
EAS		0.21			0.14			0.18	
SAS		N/A			N/A			N/A	
Others		0.14			0.27			0.23	
HWE *P*-value									
EUR		0.79			0.44			0.45	
AFR		0.42			0.73			0.77	
AMR		0.78			0.90			0.76	
EAS		0.47			0.66			0.42	
SAS		N/A			N/A			NA	
Others		0.53			0.77			0.71	

Abbreviations: A, effect allele; AFR, African American; AMR, Hispanic; C, non-effect allele; EAS, East Asian; EUR, European; HWE, Hardy-Weinberg equilibrium; N/A, too few participants to compute; SAS, South Asian.

indicate that the association between rs247617 and *CETP* results in beneficial alterations in lipid levels.

rs148323096 is an intronic indel variant in *SUCLG2*-AS1 that is an antisense RNA gene of *SUCLG2*. This is the first study showing an association between the rs148323096 and plasma triglyceride concentrations. It should be noted that the association results were in the same direction and were nominally significant in both TODAY and SEARCH individually, further validating our finding. rs14832096 is in almost complete linkage disequilibrium with 9 variants in *SUCLG2*-AS1, but all of them are intronic, and given the lack of functional studies, their consequences on gene expression or function are difficult to predict. The *SUCLG2* gene encodes a GTP-specific beta subunit of succinyl-coenzyme A (CoA) synthetase, an enzyme that catalyzes the formation of succinyl-CoA. *SUCLG2*-AS1 belongs to the group of long noncoding RNAs that are believed to regulate the transcription of the gene [20]. Although functional studies or Expression Quantitative Trait Loci for this variant are missing, one could speculate that rs148323096 in *SUCLG2*-AS1 may negatively affect the regulation of succinate-CoA synthetase by reducing its expression in the liver. Reduced hepatic expression of succinate-CoA ligase could cause an accumulation of citrate, a substrate for acetyl-CoA, which in turn can fuel de novo hepatic lipogenesis causing an increase of triglyceride synthesis and production. Kibbey et al demonstrated that succinyl-CoA synthetase might modulate glucose-induced insulin

Table 3. Clinical characteristics of the study groups by rs247617 genotype

	TODAY			SEARCH			TOTAL		
	C/C	A/C	A/A	C/C	A/C	A/A	C/C	A/C	A/A
n	287	214	38	253	200	45	540	414	83
Age (years)	14.2 ± 2.0	14.3 ± 2.0	14.6 ± 1.89	15.6 ± 2.6	15.8 ± 2.9	15.3 ± 2.8	14.9 ± 2.4	15.1 ± 2.6	15.0 ± 2.4
Sex (girls), %	67.9	59.4	60.5	60.9	60.5	66.6	64.6	59.9	63.8
z-score BMI	2.25 ± 0.46	2.17 ± 0.49	2.23 ± 0.49	2.12 ± 0.65	2.11 ± 0.67	2.14 ± 0.70	2.19 ± 0.56	2.14 ± 0.59	2.18 ± 0.61
Lipid traits									
TRIG (mg/dL)	119.8 ± 72.2	113.4 ± 94.5	95.9 ± 49.9	159.9 ± 174.2	166.1 ± 179.8	134.23 ± 96.1	138.5 ± 131.3	138.4 ± 143.8	116.3 ± 79.8
LDL-c (mg/dL)	86.0 ± 23.7	80.7 ± 24.6	85.6 ± 26.8	104.9 ± 31.7	106.4 ± 31.3	106.4 ± 36.6	94.8 ± 29.3	93.00 ± 30.8	96.8 ± 33.9
HDL-c (mg/dL)	37.3 ± 8.61	40.1 ± 8.50	41.7 ± 6.92*	39.8 ± 10.4	42.4 ± 9.57	44.1 ± 11.9	38.4 ± 9.57	41.2 ± 9.09	43.1 ± 9.93**
Lipid medication (%)	1.1%	1%	0%	2.8%	3%	0%	1.9%	1.9%	0%
Glycemic parameters									
Glucose (mg/dL)	110.9 ± 23.3	110.9 ± 25.4	103.5 ± 17.4	158.7 ± 83.3	156.0 ± 84.0	145.1 ± 66.9	133.2 ± 63.9	132.5 ± 64.9	125.9 ± 54.4
Insulin (uU/mL)	32.1 ± 22.93	30.5 ± 22.17	24.2 ± 17.07	28.5 ± 22.5	38.2 ± 45.4	29.0 ± 24.5	31.1 ± 22.8	32.7 ± 30.8	26.0 ± 20.0
HbA1c %	6.04 ± 0.78	5.99 ± 0.71	5.92 ± 0.72	7.54 ± 2.38	7.48 ± 2.28	7.42 ± 2.08	6.74 ± 1.88	6.71 ± 1.82	6.73 ± 1.77

The table shows the baseline clinical characteristics of the participants by rs247617 in SEARCH and TODAY separately and combined. Data are shown as mean and SD. $^{*}P = 0.06$; $^{**}P = 0.01$.
Abbreviations: A, effect allele; BMI, body mass index; HbA1c, hemoglobin A1c; C, non-effect allele; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; SEARCH, SEARCH for Diabetes in Youth; TODAY, Treatment Options for Type 2 Diabetes in Adolescents and Youth; TRIG, triglycerides.

secretion through GTP formation in the mitochondria [21]. Therefore, it would be interesting to test glucose-induced insulin responses in participants carrying the risk allele to assess whether this variant may play any role in the development of prediabetes and T2D in youth. A strength of our study is that this is the first large-scale study of dyslipidemia in youth with T2D. However, despite this, the sample size remains relatively small size for a GWAS limiting the power to detect more variants. Also, while our study was multiethnic, our numbers were too small for meaningful analyses separately by ancestral group. It should also be noted that participants enrolled in the SEARCH study tended to have higher lipid, glucose, and hemoglobin A1c concentrations than youth enrolled in the TODAY study (Table 1). This may be due to the different enrollment criteria of the 2 studies and because TODAY was a clinical trial while SEARCH is an observational study. Additionally, while the objective of our study was to evaluate the genetics of dyslipidemia specifically in youth with T2D, it would be important to replicate our findings in a both lean and obese pediatric cohorts without diabetes, well matched for age and sex, and divided into lean and similarly increased body mass index groups.

In conclusion, our genetic analyses of lipid traits in youth with T2D uncovered a novel association with triglycerides and a known association with HDL-c. While this study offers the first glimpse of the genetics of lipid traits in youth with T2D, increased sample size and diversity and additional functional studies are needed to further understand the genetic components of dyslipidemia in youth with T2D.

Table 4. Minor allele frequency and Hardy-Weinberg equilibrium of rs148323096 genotype in *SUCLG2-AS1* by ancestral group

	TODAY		SEARCH		Total	
	AT/AT	A/AT	AT/AT	A/AT	AT/AT	A/AT
n	521	18	479	19	1000	37
MAF						
EUR	0.048		0.037		0.043	
AFR	0.0027		0.0049		0.0038	
AMR	0.0093		0.024		0.015	
EAS	0		0.071		0.036	
SAS	0.25		N/A		0.25	
Others	0.036		0.016		0.022	
HWE *P*-value						
EUR	0.59		0.69		0.51	
AFR	0.97		0.94		0.94	
AMR	0.89		0.77		0.77	
EAS	N/A		0.84		0.89	
SAS	0.64		N/A		0.64	
Others	0.89		0.93		0.88	

Abbreviations: A/AT, risk bearing genotype with deletion of T; AT/AT, non-risk bearing genotype; EUR, European; AFR, African American; AMR, Hispanic; EAS, East Asian; HWE, Hardy-Weinberg equilibrium; MAF, minor allele frequency; N/A, too few participants to compute; SAS, South Asian.

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SEARCH for Diabetes in Youth: The SEARCH for Diabetes in Youth Study is indebted to the many youth and their families, and their health care providers, whose participation made this study possible.

Table 5. Clinical characteristics of the study groups by rs148323096 genotype

	TODAY		SEARCH		TOTAL	
	AT/AT	A/AT	AT/AT	A/AT	AT/AT	A/AT
n	521	18	479	19	1000	37
Age	14.4 ± 2.01	14.3 ± 1.87	15.6 ± 2.77	16.1 ± 2.43	15.0 ± 2.48	15.2 ± 2.3
Sex (girls %)	64.3	55.5	61.3	57.8	62.9	56.7
BMI *z*- score	2.22 ± 0.47	2.22 ± 0.47	2.12 ± 0.66	2.01 ± 0.65	2.17 ± 0.57	2.11 ± 0.57
Lipid traits						
TRIG (mg/dL)	111.9 ± 70.5	221.8 ± 203.6*	152.3 ± 140.7	350.4 ± 484.7**	131.0 ± 111.2	287.8 ± 375.9***
LDL-c (mg/dL)	83.78 ± 24.2	90.4 ± 31.2	105.9 ± 32.2	99.7 ± 23.9	94.2 ± 30.3	95.4 ± 27.7
HDL-c (mg/dL)	38.9 ± 8.64	34.9 ± 6.03	41.45 ± 10.25	35.2 ± 10.7	40.01 ± 9.52	35.1 ± 8.73
Lipid medication (%)	1%	0%	2.7%	0%	1.8%	0%
Glycemic parameters						
Glucose (mg/dL)	110.6 ± 23.9	106 ± 22.2	156.7 ± 82.3	150.8 ± 82.5	132.5 ± 63.6	129.6 ± 65.1
Insulin (uU/mL)	30.9 ± 22.5	30.4 ± 17.5	32.1 ± 33.8	40.5 ± 41.1	31.3 ± 26.1	34.2 ± 28.2
HbA1c %	6.01 ± 0.75	5.94 ± 0.68	7.53 ± 2.31	6.73 ± 2.04	6.74 ± 1.85	6.34 ± 1.57

The table shows the baseline clinical characteristics of the participants by rs148323096 in SEARCH and TODAY separately and combined. Data are shown as mean and SD. $*P = 0.03$; $**P = 0.03$; $***P = 2.26 \times 10^{-8}$.

Abbreviations: A/AT, risk bearing genotype with deletion of T; AT/AT, non-risk bearing genotype; BMI, body mass index; HbA1c, hemoglobin A1c; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; SEARCH, SEARCH for Diabetes in Youth; TODAY, Treatment Options for Type 2 Diabetes in Adolescents and Youth; TRIG, triglycerides.

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Author Contributions

L.C. conducted the analysis and edited and approved the manuscript. S.S. and N.S. assisted in forming the analyses plan, interpretation of data, manuscript writing, and edited and approved the manuscript. J.T., J.D., A.S., S.G., B.B., M.H., L.L., S.M., J.F., and S.C. assisted in forming the analyses plan, interpretation of data, and edited and approved the manuscript. J.C.F supervised analyses and interpretation of data and edited and approved the manuscript. S.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the results.

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Disclosure Summary

The authors do not have any disclosures to report.

Additional Information

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Data Availability: The data sets analyzed in the current study are publicly available in dbGap (dbGaP Study Accession: phs001511.v1.p1, https://www.ncbi.nlm.nih.gov/projects/gap/cgi-bin/study.cgi?study_id=phs001511.v1.p1). No applicable resources were generated or analyzed during the current study.

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