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Univariate and Bivariate Linkage Analysis Identifies Pleiotropic Loci Underlying Lipids and Type 2 Diabetes

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Summary

Dyslipidemia frequently co-occurs with type 2 diabetes (T2D) and with obesity. To investigate whether the co-occurrence is due to pleiotropic genes, we performed univariate linkage analysis of lipid levels and bivariate linkage analysis of pairs of lipid levels and of lipid levels paired with T2D, body mass index (BMI), and waist-hip ratio (WHR) in the African American subset of the Genetics of NIDDM (GENNID) sample. We obtained significant evidence for a pleiotropic low density lipoprotein cholesterol (LDL-C)–T2D locus on chromosome 1 at 16–19 megabases (MB) (bivariate lod = 4.41), as well as a non-pleiotropic triglyceride (TG) locus on chromosome 20 at 28–34 MB (univariate lod = 3.57). In addition, near-significant evidence supported TG–T2D loci on chromosome 2 at 81–101 MB (bivariate lod = 4.23) and 232–239 MB (bivariate lod = 4.27) and on chromosome 7 at 147–151 MB (univariate lod = 3.08 for TG with P = 0.041 supporting pleiotropy with T2D), as well as an LDL-C–BMI locus on chromosome 3 at 137–147 MB (bivariate lod score = 4.25). These finding provide evidence that at least some of the co-occurrence of dyslipidemia with T2D and obesity is due to common underlying genes.

Introduction

Dyslipidemia, most commonly elevated plasma triglyceride (TG), frequently co-occurs with type 2 diabetes (T2D) (Ginsberg et al 2005). A causal connection has been proposed: that ectopic lipid accumulation leads to insulin resistance, resulting in T2D (Savage et al 2007;

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Web Resources

jPAP http://hasstedt.genetics.utah.edu/
Eclipse2 http://www.stat.washington.edu/thompson/Genepi/Eclipse.shtml
MERLIN http://www.sph.umich.edu/csg/abecasis/Merlin
PedCheck http://watson.hgen.pitt.edu/register/docs/pedcheck.html
CIDR http://www.cidr.jhmi.edu/
GENNID http://professional.diabetes.org/Diabetes_Research.aspx?typ=18&cid=64380

Wolf 2008). Supporting a causal connection, three genes that link TG with carbohydrate metabolism have recently been identified in genome-wide association studies of TG in normolipidemic subjects: *GCKR* (glucokinase regulatory protein) (Saxena et al 2007) associated with glucose level as well as TG level (Orho-Melander et al 2008); *MLXIPL* (MLX interacting protein-like; also known as *CHREBP*) (Kooner et al 2008), a glucose-responsive transcription factor that participates in hepatic glycolysis, lipogenesis, and VLDL secretion (Uyeda & Repa 2006); and *GALNT2* (UDP-N-acetyl-alpha-D-galactosamine:polypeptide N-acetylgalactosaminyltransferase 2 (GalNAc-T2)) (Kathiresan et al 2008) which is also associated with extreme TG variation (Hegele et al 2009), but remains to be tested for T2D association. Even if only a subset of T2D results from lipid accumulation, the consideration of T2D in conjunction with lipid levels may help to dissect the genetic heterogeneity and provide clues to pathogenesis. This holds even if dyslipidemia and insulin resistance are both consequences of an alternate cause such as inflammation (Shoelson et al 2007).

Dyslipidemia also associates with obesity (Bamba & Rader 2007), including in T2D patients (Lin et al 2006). Again, the possibility of a causal connection follows from the discovery of genes associated with both dyslipidemia and obesity, such as *UCP2* (uncoupling protein 2) and *UCP3* (Salopuro et al 2009) and *GPAT3* (Glycerol-3-phosphate acyltransferase 3) and *GPAT4*, which catalyze the first step in the de novo synthesis of triglycerides and play important roles in the development of hepatic steatosis, insulin resistance, and obesity (Gimeno & Cao 2008). Nevertheless, there is considerable heterogeneity of plasma lipid profile in overweight and obese people, which has been partly attributed to the degree of visceral adiposity and insulin resistance (Mooradian et al 2008).

Although African Americans have a higher prevalence of T2D (Elbein 2007), they have a less risky lipid profile, with higher HDL-C and lower TG levels, than European Americans (Kuller 2004). In fact, African Americans are more likely to be insulin resistant and have low TG (Sumner & Cowie 2008), partly attributable to differences in body fat distribution. Obesity is more common in African American women (Ogden et al 2007), but African Americans have lower odds for combined hyperlipidemia than whites despite higher body mass index (BMI) and abdominal adiposity (Paramsothy et al 2009). Consequently, different genes may be discovered when studying lipid levels, T2D, and obesity in African Americans.

The Genetics of NIDDM (GENNID) study was established by the American Diabetes Association as a resource for the discovery of genes related to diabetes and its complications. From 1993 to 2003 the GENNID study ascertained families from multiple sites through T2D-diagnosed siblings. Linkage scans using microsatellite markers of lipids in the African American subset of the GENNID sample identified one suggestive linkage peak for total cholesterol (TC) (Malhotra & Wolford 2005) and no evidence of linkage for the lipids factor of metabolic syndrome (Edwards et al 2008).

Herein, we present univariate linkage analysis of lipid levels and bivariate linkage analysis of pairs of lipid levels and of lipid levels paired with T2D, waist-hip ratio (WHR), and BMI in the African American subset of the GENNID sample. Since the previous linkage analyses, the sample has been enlarged considerably and genotyped with single nucleotide polymorphism (SNP) markers to increase the linkage information.

Subjects and Methods

The GENNID study ascertained families through a sibling pair each with a T2D diagnosis (Raffel et al 1996). During Phase 1, extended family members were also studied; one site

ascertained African Americans. During Phase 2, data collection beyond the sibling pair was limited to parents, or, if parents were unavailable, unaffected siblings; five sites ascertained African Americans. During Phase 3, sites were added which collected only affected sibling pairs and trios. In total, 1,496 African Americans members of 580 pedigrees were studied at 10 sites. Of 530 pedigrees genotyped for this study, 221 consisted of an affected sib pair, 10 included parents, and 139 others included one or more unaffected members. This study was approved by the Institutional Review Board at each participating institution.

T2D was diagnosed using National Diabetes Data Group criteria (either fasting plasma glucose ≥140 mg/dl on 2+ occasions or plasma glucose ≥200 mg/dl at 2 hours and at a second time point of a glucose tolerance test). Age of diagnosis (AOD) was reported on a standardized questionnaire. Height, weight and waist and hip circumference were obtained from physical examination, from which WHR and BMI were computed. TC was measured enzymatically, HDL-C was measured following heparin-manganese sulfate precipitation, and TG was measured using a free-glycerol blanking method (Raffel et al 1996). Low density lipoprotein cholesterol (LDL-C) was estimated by the Friedewald equation (LDL-C = TC - HDL -TG/5) when TG < 400 mg/dl (Friedewald et al 1972).

BMI, WHR, and the lipid levels (TC, LDL-C, HDL-C, and TG) were transformed, separately in males and females, using the inverse normal distribution, for which a quantile was assigned to each trait value and the corresponding inverse normal deviate assigned as the trait. Skew and kurtosis remained minimal in all transformed variables after adjustment for gender and age.

The Center for Inherited Disease Research (CIDR) genotyped 5,958 autosomal SNPs on 1473 individuals using Illumina Linkage Panel IVb. Pedigree errors were identified using Eclipse2 (Sieberts et al 2002) and genotype errors were identified using Pedcheck (O'Connell & Weeks 1998) and MERLIN (Abecasis et al 2002). Multi-point identity by descent (IBD) probabilities were computed at each centimorgan using MERLIN (Abecasis et al 2002), treating as haplotypes SNP sets with pairwise linkage disequilibrium $r^2 > 0.70$. See Elbein et al (2009) for more details.

Likelihood analysis, as implemented in jPAP (Hasstedt, 2005), was used for univariate analysis of lipid levels and bivariate analysis of all lipid pairs, and of each lipid paired successively with T2D, BMI, and WHR. Transformed BMI, WHR, and lipid levels were each modeled as a normal density with mean μ and standard deviation σ. Gender and age were included as covariates. T2D risk was modeled to account for AOD in affected pedigree members, while allowing for censored observations, through a modification of the age-of-onset regressive logistic model (Elston & George 1989), also known as the age at diagnosis regressive model, and described as Method 2 in Cui et al (2003). Let W represent AOD or age last examined if unaffected, and X=0/1 for male/female. The logit of the probability of T2D equals

$$\text{logit}\,[\pi(w, x)]=\alpha+\beta w+\gamma x$$

where $\pi(w, x)=\Pr(T=1|W=w, X=x)$ denotes the probability of T2D, $p=\ln(\alpha/(1-\alpha))$ represents male lifetime penetrance, $\exp(\beta$ represents the annual odds ratio (OR) due to age, and $\exp(\gamma)$ represents the female/male OR. In addition, each univariate model included a polygenic effect (h^2 or heritability) and a quantitative trait locus (QTL) effect (q^2). Each bivariate model included h^2_i and q^2_i for trait i=1,2, as well as the correlations between the traits: ρ_q or pleiotropy, between QTL effects, ρ_g or the genetic correlation between polygenic effects,

and ρ_e, the residual environmental correlation. Parameters were estimated as the values that maximized the likelihood.

To estimate heritability and the genetic and environmental correlations, we used the univariate and bivariate models setting $q^2 = 0$ or $q^2_1 = q^2_2 = \rho_q = 0$, respectively. In the univariate T2D and bivariate lipid–T2D analyses, we corrected the likelihood for the ascertainment of each pedigree through an affected sib pair. To perform autosome-wide variance components linkage analysis, we used the univariate and bivariate models in conjunction with the IBD probabilities. All the parameters of the models were estimated every cM except for p, β and γ in the univariate T2D and bivariate lipid–T2D analyses. In those analyses, p, β and γ were fixed at estimates obtained upon maximizing the likelihood of the linkage analysis model with $q^2 = 0$ or $q^2_1 = q^2_2 = \rho_q = 0$ while correcting the likelihood for the ascertainment of each pedigree through an affected sib pair. Ascertainment correction was not made in any linkage analyses.

Hypotheses were tested through comparison of the maximized likelihoods of general and nested models. Asymptotically, and under certain regularity conditions, twice the natural logarithm of the likelihood ratio distributes as a χ^2, or as a mixture of χ^2 for a 1-tailed test when the nested model constrains a parameter at its boundary (Self & Liang 1987). Alternatively, we computed the lod score as the common logarithm of the likelihood ratio; support intervals for both univariate and bivariate linkages are presented as megabase (MB) 1-lod drop intervals. The test of significant heritability, that $h^2 = 0$, used the univariate model with $q^2 = 0$ and distributed as a 1/2:1/2 mixture of a χ^2 with 1 degree of freedom and a point mass at zero. The test of significant genetic, or environmental correlation, that $\rho_g = 0$ or $\rho_e = 0$, used the bivariate model with $q^2_1 = q^2_2 = \rho_q = 0$ and distributed as a χ^2 with 1 degree of freedom. Univariate linkage tested $q^2 = 0$ and distributed as a 1/2:1/2 mixture of a χ^2 with 1 degree of freedom and a point mass at zero. Bivariate linkage tested $q^2_1 = q^2_2 = \rho_q = 0$ and distributed as a 1/4:1/2:1/4 mixture of a χ^2 with 3 and 1 degrees of freedom and a point mass at zero (Amos et al 2001). The test of a single QTL effect, that $q^2_1 = \rho_q = 0$ or $q^2_2 = \rho_q = 0$, used the bivariate model and distributed as a 1/2:1/2 mixture of a χ^2 with 2 degree of freedom and a point mass at zero. The test of significant pleiotropy or QTL correlation, that $\rho_q = 0$, used the bivariate model and distributed as a χ^2 with 1 degree of freedom. To account for multiple testing, autosome-wide statistics were considered significant (0.05 false positives expected per scan) if $P < 0.00005$, near-significant (0.1 false positives expected per scan) if $P < 0.0001$ and suggestive (one false positive expected per scan) if $P < 0.001$. Since SNP panels require higher thresholds than microsatellites (Wilcox et al 2005), these probabilities are intermediate between those for 400 markers and a continuous map (Rao & Gu 2001). The corresponding significant, near-significant, and suggestive lod scores were 3.29, 3.00 and 2.07 for univariate analysis and 4.31, 4.00, and 2.95 for bivariate analysis. At each inferred univariate lipid locus, QTL effects were tested for three traits (T2D, BMI, and WHR). Therefore, $P < 0.05/3 = 0.0167$ and $P < 0.1/3 = 0.0333$ were considered significant and near-significant, respectively. For pleiotropy, tested only for significant QTL effects, $P < 0.05$ and $P < 0.1$ were considered significant and near-significant, respectively.

Results

The sample comprised 81% T2D cases and 65% women (Table 1). T2D cases were older and had higher levels of BMI, WHR, TC, and TG and lower levels of HDL-C. Only for LDL-C were lower-risk levels observed in T2D cases: median LDL-C level was lower in both male and female cases and mean LDL-C level was lower in male cases. However the differences were small and LDL-C levels were uncorrected for treatment with lipid-lowering drugs as that information was not available.

All traits except T2D were significantly heritable (Table 2); ascertainment correction reduced the heritability of T2D. The genetic correlation attained significance for BMI with T2D, WHR, and HDL-C, for TC with all other lipids, and for HDL-C with TG. Environmental correlations attained significance for TG with all other traits, for WHR with T2D, BMI, and HDL-C, and for TC with LDL-C.

TG produced the strongest linkage evidence with one significant, one near-significant, and three suggestive lod scores (Table 3); each of the other lipids produced only one suggestive lod score. Most locations supported linkage for a single lipid. One exception occurred on chromosome 5 where suggestive lod score peaks for HDL-C and TG overlapped

Using bivariate analysis, we tested for pleiotropic effects on T2D, BMI, and WHR of each of the lipid loci identified through univariate linkage analysis (Table 3). Pleiotropy attained significance for two loci: with BMI for the suggestive chromosome 1 TG locus and with T2D for the near-significant chromosome 7 TG locus. Pleiotropy attained near-significance for two loci: with WHR for the suggestive chromosome 5 HDL-C locus and with BMI for the suggestive chromosome 10 LDL-C locus. Chromosome 20, with a significant TG lod score and near-significant QTL effect for T2D, but non-significant pleiotropy, may harbor adjacent, but non-identical, T2D and TG genes.

In another approach, we identified pleiotropic loci through bivariate lod scores; significance thresholds were also required for both QTL effects to ensure the contribution of both traits to the lod score (Table 4). Eight loci provided evidence of pleiotropy, four supported by significant or near-significant lod scores (Table 4). The only lipid–lipid lod scores were suggestive HDL-C–TG loci, including the chromosome 5 locations that produced suggestive univariate lod scores for HDL-C and TG (Table 3). Otherwise, all suggestive loci paired lipids with T2D or BMI; no lipid–WHR lod scores produced suggestive linkage evidence.

Discussion

The frequent co-occurrence of dyslipidemia with T2D and/or obesity may result from common underlying genes, common underlying environmental factors, or from a causal chain leading from one to the other. This analysis supported the existence of common underlying genes by providing evidence of three pleiotropic TG–T2D loci and one pleiotropic LDL-C–T2D locus. That TG most often showed pleiotropy with T2D is consistent with T2D having a higher genetic correlation with TG than with the other lipids and with hypertriglyceridemia being the primary dyslipidemia associated with T2D (Ginsberg et al 2005). Apleiotropic LDL-C–BMI locus was also inferred.

Three of the pleiotropic loci identified using bivariate linkage analysis (chromosomes 1 at 16–19 MB, 2 at 81–101 MB, and 3 at 137–147 MB) were previously reported in univariate linkage analysis of T2D or BMI (Elbein et al 2009), although none attained significance. Nevertheless, bivariate analysis not only strengthened support for the loci, but also inferred an effect on LDL-C or TG. Another TG–T2D locus (chromosome 2 at 234–140 MB) was not detected in univariate linkage analysis of either TG or T2D. An alternate strategy, detecting loci through univariate linkage scans of lipids, then testing each locus for pleiotropy with T2D, BMI, and WHR, yielded another near-significant TG–T2D locus (chromosome 7 at 147–151 MB); TG linkages to the same location in other samples (Duggirala et al 2000; Shearman et al 2000; Sonnenberg et al 2004; Li et al 2005) strengthen the evidence supporting this locus. The initial detection of the chromosome 7 locus through univariate linkage to TG may reflect a more moderate effect on T2D risk than the TG–T2D loci detected through bivariate analysis. The univariate linkage scan also yielded one significant TG locus without evidence of pleiotropy (chromosome 20 at 20–38 MB).

A number of genetic variants have well-established effects on TG levels (Hegele 2009), but none of those genes fall in our linkage regions. The evidence of pleiotropy leads us to expect both chromosome 2 genes and the chromosome 7 gene to affect T2D risk as well as TG levels, while we expect the chromosome 20 gene to affect only TG level. On chromosome 2 near 84 MB, *FABP1* (fatty acid binding protein 1, liver) T94A polymorphism associated with TG level (Fisher et al 2007) as well as hyperglycemia (Weickert et al 2007). On chromosome 2 near 238 MB, *CAPN10* (calpain-10), initially identified from a T2D linkage (Horikawa et al 2000), associated with TG levels as well (Carlsson et al 2004). On chromosome 7, the nitric oxide synthase 3 (*NOS3*) G894T polymorphism associated with metabolic syndrome, which encompasses dyslipidemia and T2D (Piccoli et al 2008). Chromosome 20 lacks obvious candidates.

The identification of pleiotropic TG–T2D loci is consistent with the substantial genetic correlation between TG and T2D, since genetic correlation implicates pleiotropic genes. However, those genes may be undetectable if the correlation results from multiple genes each with a small effect size. BMI correlated significantly with HDL-C and TG correlated significantly with WHR, but no significant HDL-C–BMI or TG–WHR loci were identified. The strongest evidence for a lipid–obesity locus was a LDL-C–BMI locus on chromosome 3.

Chromosome 7 at 149 MB is the only region of overlap of our significant or near-significant loci with TG loci detected in other linkage scans (Seda 2004). For our suggestive loci, the chromosome 19 TC locus is the only region of overlap with significant or suggestive lipid linkages in meta-analysis of T2D-ascertained families (Malhotra et al 2007). No overlap was observed with results of meta-analysis of linkage studies in African Americans (Malhotra et al 2005) or in African T2D-ascertained families (Adeyemo et al 2005). Therefore, this analysis has identified unique linkages.

In summary, variance components linkage analysis provided significant evidence for one pleiotropic LDL-C–T2D locus and one TG–only locus, as well as near-significant evidence for three pleiotropic TG–T2D loci and one pleiotropic LDL-C–BMI locus. Identification of the underlying genes should both increase understanding of the pathogenesis of dyslipidemia and T2D and aid the dissection of the genetic heterogeneity of T2D. In addition, this analysis demonstrated the value of deeper systematic analysis of well-characterized data sets by identifying loci that were undetectable using traditional analysis. In addition to linkage analysis, genome-wide association and resequencing efforts would also undoubtedly profit from deeper analysis.

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Table 1

Characteristics of the sample by gender and T2D status.

Variable	Gender	T2D Status	N	Mean	SD	Minimum	Median	Maximum
Age (yrs)	Male	Affected	388	54.12	11.90	19	54	92
		Unaffected	109	50.33	16.35	18	49	90
	Female	Affected	778	54.48	12.10	20	55	96
		Unaffected	166	51.06	15.60	20	51	95
BMI(kg/m^2)	Male	Affected	378	30.58	6.01	16.75	29.89	55.27
		Unaffected	109	28.31	6.21	17.86	27.77	55.90
	Female	Affected	753	34.43	7.97	16.84	33.30	64.51
		Unaffected	155	33.03	7.91	17.28	32.65	55.93
WHR (%)	Male	Affected	319	97.45	7.78	78.99	96.82	138.33
		Unaffected	89	91.99	7.30	77.14	91.48	125.95
	Female	Affected	701	93.46	10.14	54.37	92.61	137.31
		Unaffected	136	87.85	9.36	66.47	87.25	127.38
TC (mg/dL)	Male	Affected	361	194.26	47.47	62	189	407
		Unaffected	105	186.75	38.70	103	188	300
	Female	Affected	718	194.44	44.51	43	192.5	396
		Unaffected	156	187.04	39.21	92	188.5	290
LDL-C (mg/dL)	Male	Affected	343	126.36	40.83	31	124	316
		Unaffected	105	127.08	36.73	48	127.8	237.8
	Female	Affected	705	124.95	38.33	27	123	328
		Unaffected	155	121.51	37.63	29.2	124	217
HDL-C (mg/dL)	Male	Affected	361	40.24	11.94	14	39	82
		Unaffected	105	43.59	13.54	20	42	102
	Female	Affected	718	47.11	14.51	9	45	111
		Unaffected	156	49.76	12.72	25	49	113
TG (mg/dL)	Male	Affected	361	146.06	148.41	30	106	1432
		Unaffected	105	80.52	41.51	24	67	207
	Female	Affected	718	114.62	86.30	19	90	932

Variable	Gender	T2D Status	N	Mean	SD	Minimum	Median	Maximum
		Unaffected	156	78.58	56.79	16	66	521

Table 2

Estimates (%) of heritability (h^2, diagonal in bold), genetic correlation (ρ_g, above the diagonal), and environmental correlation (ρ_e, below the diagonal).

Trait	T2D	BMI	WHR	TC	LDL-C	HDL-C	TG
T2D	**11.21**	76.96***	7.94	−8.05	−14.02	−12.25	44.48
BMI	17.90	**51.39***	61.10***	0.96	10.08	−25.68*	11.10
WHR	41.35***	39.17***	**39.56*****	13.92	16.35	−20.03	29.51*
TC	11.53	6.30	4.54	**55.40*****	94.36***	30.73**	36.43**
LDL-C	3.51	3.40	2.71	91.84***	**52.96*****	12.72	16.79
HDL-C	−10.33	−18.66	−18.09*	6.57	−8.80	**51.12*****	−26.47*
TG	28.08***	23.73**	22.04**	39.85***	27.23**	−47.49***	**41.31*****

*P< 0.05

**P< 0.01

***P<0.001

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Table 3

Univariate lod scores > 2.07 (suggestive) for linkage to lipid levels. At the same location, P-values for the QTL effects (q^2_2) for T2D, BMI, and WHR and for pleiotropy (ρ_q) between the QTL effects of the lipid and T2D, BMI, and WHR from bivariate linkage analysis.

Chromosome	Position (MB)[1]	Lipid	Lod[2]	P-Value[3]					
				T2D		BMI		WHR	
				q_2^2	ρ_q	q_2^2	ρ_q	q_2^2	ρ_q
1	202–209	TG	2.97	0.364	0.751	**0.0150**	**0.0301**	0.128	0.257
4	99–113	TG	2.35	0.0572	0.439	1.00	1.00	0.444	0.887
5	12–32	HDL-C	2.49	0.113	0.225	0.149	0.298	*0.0265*	*0.0541*
5	29–32	TG	2.72	0.0766	0.153	1.00	1.00	0.0688	0.138
7	147–151	TG	*3.08*	*0.0203*	**0.0407**	0.143	0.353	0.0496	0.117
10	87–108	LDL-C	2.29	0.0776	0.155	**0.0160**	*0.0560*	0.450	0.901
19	29–38	TC	2.13	0.349	0.698	0.213	0.975	0.290	0.581
20	20–38	TG	**3.57**	*0.0192*	0.886	0.0624	0.469	0.104	0.560

[1] 1-lod drop support interval in megabases, Build 37.1

[2] Significant (>3.29, bold) and near-significant (>3.00, italics) univariate lod scores.

[3] For q_2^2, Significant (<0.0167, bold) and near-significant (<0.0333, italics) P-values. For ρ_q, significant (<0.05, bold) and near-significant (<0.1, italics) P-values.

Table 4

Bivariate lod scores > 2.95 (suggestive) for which QTL effects for both traits (q^2_1 and q^2_2) were at least suggestive (P < 0.001).

Chromosome	Position (MB)[1]	$Trait_1$	$Trait_2$	Lod[2]	P-Value[3]		P-Value
					q_1^2	q_2^2	ρ_q
1	16–19	LDL-C	T2D	**4.41**	0.000348	**0.00000814**	0.00180
2	81–101	TG	T2D	*4.23*	0.000377	**0.00000515**	0.000755
2	232–239	HDL-C	TG	3.07	0.000138	0.000164	0.000389
2	234–240	TG	T2D	*4.27*	0.000192	*0.0000522*	0.00284
3	137–147	LDL-C	BMI	*4.25*	0.000372	0.000201	0.0364
5	18–32	HDL-C	TG	3.92	0.000147	0.000243	0.00425
13	28–34	TC	BMI	3.29	0.000220	*0.0000578*	0.000529

[1] 1-lod drop support interval in megabases, Build 37.1

[2] Significant (>4.31, bold) and near-significant (>4.00, italics) univariate lod scores.

[3] Significant (<0.00005, bold) and near-significant (<0.0001, italics) P-values.