Genetic Predisposition for Hypertriglyceridemia is Modified by Extremes of Adiposity

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Introduction

The Global Lipids Genetics Consortium identified 95 common loci that explain 12.2% (LDL-C), 12.1% (HDL-C) and 9.6% (TG) of total variance in plasma lipid traits in the Framingham Heart Study.

In addition to genetically based variation in genes regulating plasma lipid metabolism, circulating concentrations of TGs, LDL-C and HDL-C are affected by environmental factors. Increasing adiposity is associated with higher levels of plasma triglycerides and lower levels of HDL-C. It is unknown whether body mass index (BMI) attenuates or exacerbates genetic predisposition for these lipid traits.

Here, we examined whether the effects of a weighted genetic risk score (GRS) for LDL, HDL, and TG, are modified by adiposity. Specifically, we determined whether obesity exacerbates the aggregated, weighted risk of 95 lipogenic loci.

The study was carried out in two independent cohorts: Obese vs. Lean (OBLE) recruited in Ottawa and CAD Controls (CC) recruited as part of the Ottawa Heart Study, Cleveland Clinic Gene Bank study or Duke Cathgen Study. All subjects were of European descent. 33 SNPs were used to analyze HDL in the CAD cohort, whereas 30 were used in the OBLE cohort. 19 SNPs were used when analyzing CAD TG, and 17 were used for OBLE. HDL-C SNPs were protective.

Methods

The study population consisted of two independent cohorts of subjects of European descent, genotyped on the Affymetrix 6.0 array with 1000G imputation.

1)OBLE: 959 obese/869 lean; BMI (mean (SD) 43.1 (8.7) vs. 20.3 (1.8) kg/m^2.

2)CC (healthy elderly subjects recruited as controls for a CAD study) 830 obese/1,044 lean; BMI 35.9 (4.6) vs. 21.5 (1.6) kg/m^2). Duke University N = 667, Cleveland Clinic N = 368.

3)Samples were genotyped at the University of Ottawa Heart Institute. Samples were run on the Affymetrix 6.0 Human SNP Array.

4)Each of the SNPs were coded as 0, 1, or 2, to represent the number of risk alleles. The aggregated risk score was calculated by taking an average of the sum across SNPs coded 0, 1, or 2 (non missing) and multiplying this by effect size observed by the Global Lipids Consortium.[vi,].

5)Multiple linear regression models were used to analyze the data. The trait values were adjusted for sex, age, pc1, and pc2. We did not assume additive effect of alleles, and instead opted to use a weighted predisposition score. Scoring and association was performed by adding up the number of trait increasing alleles and multiplying by the effect score across alleles.

6)Scoring and association were performed in PLINK, and covariate adjusted general linear models were performed in R version 3.0.1.

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Study Population

		n (OB/LE)	M	F	Age (y)	BMI (kg/m2)	Risk Score
OBLE Study							
TG	n	758 / 866	1080	544	44.7 ± 12.9	31.1±13.1	-0.202 ± 0.407
	OB		555	203	45.0 ± 10.5	43.3 ± 8.9	-0.213 ± 0.399
	LE		525	341	44.4 ± 14.7	20.3 ±1.8	-0.192 ± 0.414
LDL	n	728 / 865	1065	528	44.7 ± 13.0	30.8 ±13.0	0.228 ± 0.315
	OB		540	188	45.1 ± 10.5	43.3 ± 8.8	0.227 ± 0.311
	LE		525	340	44.4 ± 14.7	20.3 ±1.8	0.229 ± 0.319
HDL	n	866 / 753	1079	540	44.7 ± 12.9	31.0±13.0	0.007 ± 0.052
	OB		554	199	45.1± 10.5	43.3± 8.9	0.005 ± 0.051
	LE		525	341	44.4 ± 14.7	20.3 ± 1.8	0.009± 0.052
CAD Controls							
		n	M	F	Age (y)	BMI (kg/m2)	Risk Score
TG	n	2967	1466	1500	74.9 ± 5.3	26.3± 4.3	-0.149± 0.312
	OB	338	157	181	73.4±4.5	34.6± 3.2	-0.145±0.293
	LE	788	292	496	75.8±5.8	21.6±1.6	-0.142±0.316
LDL	n	2897	1429	1468	74.9±5.3	26.3± 4.3	0.320±0.233
	OB	325	150	175	73.5±4.5	34.7±3.3	0.297±0.258
	LE	774	288	486	75.7±5.8	21.6±1.6	0.331±0.235
HDL	n	2937	1448	1489	74.9±5.3	26.3±4.3	-0.006±0.040
	OB	498	240	258	73.4±4.5	34.7±3.2	-0.006±0.039
	LE	596	194	402	75.8±5.8	21.6±1.6	-0.006±0.038±

Figure 1. Description of the two study populations. Of the 3,891 CAD controls, 768 met the criterion for obesity (BMI≥30 kg/m^2) and 783 met the criterion for lean (BMI≤23kg/m^2). All subjects were of European white ancestry.

Beta GRS mmol/L

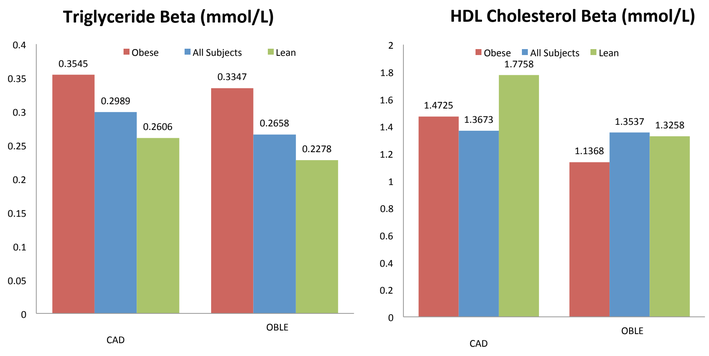

Figure 2. Beta coefficient and R^2 values were compared in multiple populations. The beta coefficients for the obese populations were found to be higher for plasma triglycerides, and lower for HDL-C. Explained variance was higher for triglycerides in obese cohorts, and higher of HDL-C in lean populations. Analysis was carried out using covariate adjusted multiple linear regression in R v. 3.0.1. a) Triglyceride data analyzed through multiple linear regression. Separated by cohort. b) HDL Cholesterol analyzed through multiple linear regression, Separated by Cohort.

TG & HDL-C vs GRS in Obese vs Lean

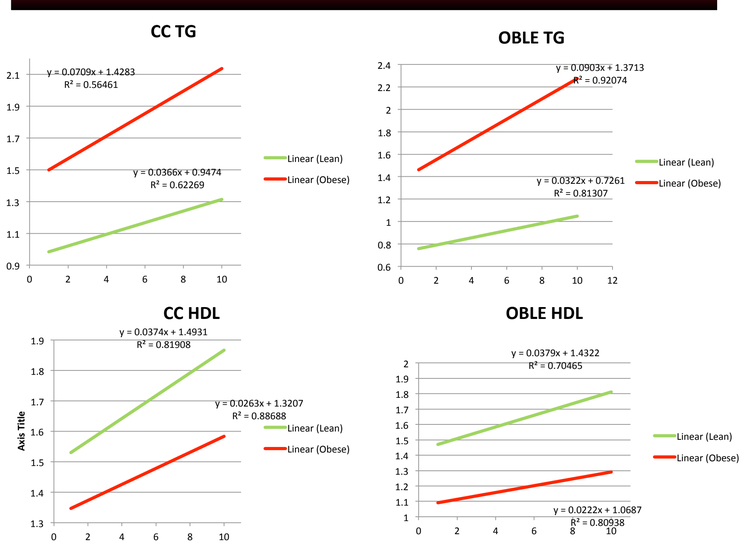

Figure 3. Visual representation of decile values of populations. Grouped by cohort. Data was generated through covariate adjusted multiple linear regression in R v. 3.0.1. a) Decile analysis of TGs line for obese vs lean in CC cohort b) Decile analysis of TGs in OBLE cohort. c) Decile analysis of HDL-_C in CC cohort. d) Decile analysis of HDL-C in OBLE cohort.

Variance in TG & HDL-C Explained by GRS

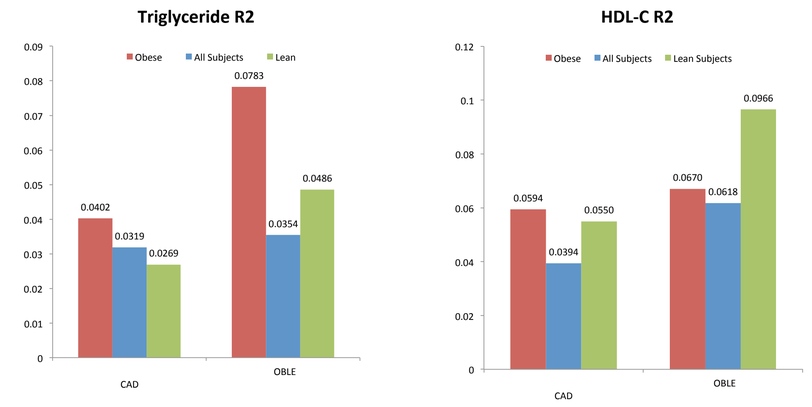

Figure 4. Explained variance (R^2) values corresponding to the multiple linear regressions in figure 1. Observe the greater variance explained in OB groups for TG, and the greater variance explained by LE in HDL. a) Explained variance (R^2) value for TG values in multiple linear regression. b) Explained variance (R^2) values for HDL Cholesterol in multiple linear regression.

Individual SNP Associations

Whole Population				Obese		Lean	
SNP	Gene	Beta	P-Value	Beta	P-Value	Beta	P-Value
Rs964184 (OBLE)	*APOA5*	0.2625	1.29E-09	0.5895	4.21E-04	0.2767	7.47E-04
rs1260326	*GCKR*	0.1172	1.01E-04	0.1325	0.011	0.05313	0.011
rs17145738	*MLXIPL*	-0.1375	0.003	-0.1842	0.020	-0.09025	0.005
rs1495741	*NAT2*	0.09365	0.008	0.139	0.024	0.05301	0.033
rs964184 (CAD)	*APOA5*	0.2098	2.20E-06	0.3235	3.54E-05	0.1145	1.90E-04

TG Individual SNP Analysis using Plink[2]

Whole Population				Obese		Lean	
SNP	Gene	Beta	P-Value	Beta	P-Value	Beta	P-Value
rs1532085	*LIPC*	0.05887	1.06E-06	0.06483	1.61E-06	0.05133	0.005
rs3764261	*CETP*	0.09707	3.09E-14	0.06559	3.34E-06	0.1223	1.74E-10

HDL Individual SNP Analysis using Plink[2]

Figure 5. Statistically significant associations between individual SNPs and trait. Adjusted for sex, age, pc1, and pc2. a) Individual TG SNPs. b) Individual HDL SNPs. To further investigate this trend we examined individual SNPs contributing to the scores using another covariate adjusted GLM this time taking into account the confounding terms sex, age, BMI, principal component (pc) 1, and pc 2.

Summary & Conclusions

Regression coefficients were higher for TGs for both cohorts of obese versus lean subjects and a weighted genetic risk score explained variance (R^2) for triglycerides to a greater extent in obese vs lean.

Several individual SNPs, rs964184 (*APOA5*), rs1260326 (*GCKR*), rs17145738 (*MLXIPL*) and rs1495741 (*NAT2*) exhibited a greater effect size for TG in obese vs lean subjects.

Conversely, regression coefficients were significantly higher for HDL-C in lean vs obese lean populations.

The *CETP* SNP, r33764261, exhibited a greater effect size for HDL-C in lean vs obese.

Genetic risk scores for each lipid trait showed no association with BMI (P>0.2) indicating that the findings are not due to possible overlap between genetic loci for BMI and lipid traits.

Genetic predisposition to elevated plasma triglycerides and low HDL-C is sensitive to extremes of BMI.

References

1.Teslovich TM et al. Nature. 2010 ;466:707-13 .
2.Purcell S et al. Am J Hum Genet 2007;81:559-575

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