Interaction of Insulin Resistance and Related Genetic Variants With Triglyceride-Associated Genetic Variants

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Background—Several studies suggest that some triglyceride-associated single-nucleotide polymorphisms (SNPs) have pleiotropic and opposite effects on glycemic traits. This potentially implicates them in pathways such as de novo lipogenesis, which is presumably upregulated in the context of insulin resistance. We therefore tested whether the association of triglyceride-associated SNPs with triglyceride levels differs according to one’s level of insulin resistance.

Methods and Results—In 3 cohort studies (combined n=12,487), we tested the interaction of established triglyceride-associated SNPs (individually and collectively) with several traits related to insulin resistance, on triglyceride levels. We also tested the interaction of triglyceride SNPs with fasting insulin–associated SNPs, individually and collectively, on triglyceride levels. We find significant interactions of a weighted genetic risk score for triglycerides with insulin resistance on triglyceride levels ($P_{interaction}=2.73\times10^{-11}$ and $P_{interaction}=2.48\times10^{-11}$ for fasting insulin and homeostasis model assessment of insulin resistance, respectively). The association of the triglyceride genetic risk score with triglyceride levels is >60% stronger among those in the highest tertile of homeostasis model assessment of insulin resistance compared with those in the lowest tertile. Individual SNPs contributing to this trend include those in/near $GCKR$, $CILP2$, and $IRS1$, whereas $PIGV-NROB2$ and $LRPAP1$ display an opposite trend of interaction. In the pooled data set, we also identify a SNP–by–SNP interaction involving a triglyceride-associated SNP, rs4722551 near $MIR148A$, with a fasting insulin–associated SNP, rs4865796 in $ARL15$ ($P_{interaction}=4.1\times10^{-5}$).

Conclusions—Our findings may thus provide genetic evidence for the upregulation of triglyceride levels in insulin-resistant individuals, in addition to identifying specific genetic loci and a SNP–by–SNP interaction implicated in this process. (Circ Cardiovasc Genet. 2016;9:154-161. DOI: 10.1161/CIRCGENETICS.115.001246.)

Key Words: genetics ▪ insulin resistance ▪ lipogenesis ▪ triglycerides

Insulin resistance is a major early risk factor for cardiometabolic disease. The various mechanisms linking insulin resistance to lipid levels and type 2 diabetes mellitus (T2DM) are still unclear.¹

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Through meta-analysis of genome-wide association studies, >30 single-nucleotide polymorphisms (SNPs) have been identified as being associated with triglyceride levels.²,³ These associations seem to be accentuated in the context of obesity.⁴⁻⁷ However, recent findings suggest that alleles associated with increased triglyceride are also associated with a decreased risk of T2DM,⁸⁻¹⁰ potentially implicating de novo lipogenesis in the liver or adipose tissue as a responsible mechanism for this seemingly paradoxical association. Because de novo lipogenesis is likely upregulated in the context of insulin resistance,¹⁰⁻¹⁴ converting glucose into fatty acids, it is possible that the triglyceride genes which are implicated in de novo lipogenesis are upregulated in the context of insulin resistance.

We tested the hypothesis that the association of triglyceride-associated loci with triglyceride levels is accentuated, independently of adiposity, among those who are in a state of insulin resistance, which we operationalize via various phenotypic and genetic measures. In 3 cohorts of Americans of European descent, we test the interaction of a genetic risk score (GRS) for triglyceride, and individual triglyceride-associated loci, with proxy phenotypic and genetic measures of insulin resistance, on triglyceride levels.

Methods

Studies

We used data from 3 population-based cohort studies in which measurements of triglycerides, high-density lipoprotein cholesterol (HDL-C), fasting insulin (FI), fasting glucose (FG), and waist/hip ratio (WHR) were available: the Atherosclerosis Risk in Communities (ARIC; n=7872), the Offspring cohort (Examination 5) of the Framingham Heart Study (FHS; n=2659), and the Multi-Ethnic Study of Atherosclerosis (MESA; n=1956).¹⁴ We included only individuals who self-reported as White. We obtained approval for this study from the University of Arizona Institutional Review Board, and we obtained data from the database of Genotypes and Phenotypes (dbGaP), through accession numbers: phs000007.v23.p8, phs000280.v2.p1, and phs000209.v10.p2.
Phenotypic Measures
We excluded subjects with prevalent T2DM, which is defined as FG levels >125 mg/dL, a report of clinical diagnosis, or taking any T2DM-related medication. We also excluded subjects who did not report fasting for at least 8 hours before the baseline examination or were on cholesterol medications. The blood samples were withdrawn for lipid and glycemic analysis at the baseline examination (at examination 5, in the case of FHS) and were stored, processed, and analyzed using standardized laboratory protocols and procedures, the details of which have been described elsewhere.23–25 Different units were used by the different studies to report/provide values of insulin resistance (HOMA-IR)22 was calculated separately, after converting each of these variables as appropriate (Data Supplement). Body mass index (BMI) was calculated as kg/m², and WHR was calculated as the ratio of waist to hip circumference.

Genotypes and GRSs
Details of study-specific genome-wide genotyping can be found elsewhere.23–25 We performed whole-genome imputation on each dataset separately after standard quality-control procedures. We used IMPUTE2 data and all individuals from the 1000 Genomes data as reference data.26 Imputation in FHS was performed based on the 1000 Genomes phase 1 interim release, whereas imputation in MESA and ARIC was performed more recently, and thus based on the 1000 Genomes phase 1 interim release, whereas imputation in FHS was performed based on the 1000 Genomes phase 1 v3 release. We considered sets of 32 and 40 SNPs robustly associated with triglyceride, HDL-C, FG, and FG (Table 1). The homeostasis model assessment of insulin resistance (HOMA-IR)27 was calculated separately in each study as the product of FI (mU/L) and FG (mg/dL), divided by a constant, after converting each of these variables as appropriate (Data Supplement). Body mass index (BMI) was calculated as kg/m², and WHR was calculated as the ratio of waist to hip circumference.

Table 1. Participant Characteristics by Study, Values Are Presented as Mean±SD, Except for % Female

|                      | ARIC (n=7872) | FHS (n=2659) | MESA (n=1956) | P Value for Differences Across Studies |
|----------------------|--------------|--------------|---------------|---------------------------------------|
| Age (y)              | 54 (±6)      | 54 (±10)     | 62 (±10)      | <2.20E-16                             |
| Sex (% female)       | 54%          | 54%          | 54%           | 0.91                                  |
| BMI (kg/m²)          | 26.7 (±4.6)  | 27.1 (±4.8)  | 27.3 (±5.0)   | 8.24E-10                              |
| Waist/hip ratio      | 0.92 (±0.07) | 0.89 (±0.09) | 0.91 (±0.08)  | <2.20E-16                             |
| FI (mU/L)            | 9.99 (±7.09) | 8.61 (±7.62) | 8.60 (±5.00)  | 0.03                                  |
| Fasting glucose (mg/dL) | 98.6 (±9.0) | 94.9 (±9.6)  | 87.4 (±9.9)   | 4.21E-06                              |
| HOMA-IR              | 2.42 (±1.92) | 2.07 (±1.96) | 1.90 (±1.27)  | 1.12E-03                              |
| Plasma triglyceride (mg/dL) | 129 (±76)  | 137 (±96)    | 127 (±73)     | 0.05                                  |
| Plasma HDL-cholesterol (mg/dL) | 51.6 (±16.8) | 51.2 (±15.2) | 53.4 (±16.2)  | 0.20                                  |
| TG GRS–32 SNP        | 154 (±16)    | 161 (±17)    | 155 (±16)     | <2.20E-16                             |
| FI GRS               | 0.32 (±0.04) | 0.31 (±0.04) | 0.32 (±0.04)  | 5.43E-03                              |

ARIC indicates Atherosclerosis Risk in Communities; BMI, body mass index; FHS, Framingham Heart Study; FI, fasting insulin; GRS, genetic risk score; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; MESA, Multi-Ethnic Study of Atherosclerosis; SNP, single-nucleotide polymorphism; TG, triglyceride; and WHR, waist/hip ratio.

Statistical Analyses
Differences in demographic and phenotypic characteristics across studies were tested using ANOVA or χ² test. We used multiple linear regression models to test associations and interactions. Within each study, we log-transformed FI, FG, triglyceride, HDL-C, and BMI to approximate a normal distribution and fulfill the assumption of normally distributed residuals. For the analyses in which we combined data across all studies, we also standardized (mean of 0 and SD of 1) triglyceride, HDL-C, FG, and FI, separately in each study, before combining them. We used sex, age, BMI, HDL-C, and WHR (measured at the first examination in ARIC and MESA, and at the fifth examination in FHS) as covariates in all of our statistical models (WHR not included as a covariate when it is the outcome variable), as well as a 3-level, categorical, study variable, modeled as a random effect, to account for variation across the 3 studies. We also considered the addition of age-squared as a covariate to account for the potential nonlinear association between age and triglyceride. HDL-C and WHR were included as covariates to avoid confounding because some triglyceride-associated SNPs are also associated with these phenotypes. Interactions were tested by including in the model the product of the triglyceride GRS or triglyceride SNP with either FI, HOMA-IR, FG, or WHR, as well as their respective main effects. Statistical significance of interactions was assessed from the parameter estimate and SE of the interaction term. For the interaction of triglyceride SNPs with glycemic and insulin resistance phenotypes, we considered a Bonferroni correction for 40 tests performed, resulting in an α=1.25×10⁻³. For the interaction of triglyceride SNPs with FI SNPs, we considered a Bonferroni correction for 520 (40×13) pairwise SNPs tests, resulting in an α=9.61×10⁻⁶. We considered this many triglyceride SNP–by–FI SNP interaction tests because some of the triglyceride-FI SNP pairs were highly correlated (r>0.80), as some loci are both triglyceride and FI associated. These include the following FI-associated SNPs (which are also...
triglyceride-associated loci): rs780094 (GCKR), rs2745353 (RSPO3), rs2943645 (IRS1), and rs731839 (PEPD). Finally, we considered 3 sensitivity analyses. Because FHS is a family-based study, we considered analyses in which we used pedigree information to include an adjustment for relatedness in a linear mixed model implemented in the package coxme in R Statistical Software.24 We also considered analyses in the absence of adjustment for the covariates BMI, WHR, and HDL-C. Finally, we also conducted interaction analyses using both the 32- and 40-SNP triglyceride GRS. All statistical analyses were conducted with R.

Results

Characteristics of the studies and their participants are shown in Table 1. Mean age and BMI are higher in the MESA cohort, whereas WHR is lowest in FHS. There are differences in the glycemic and lipid traits across studies, potentially because of slightly different measurement methodologies, among other factors. We first tested the association of each triglyceride GRS with triglyceride levels (each triglyceride GRS was standardized to facilitate comparison). In the pooled/combined data set, we find that the association of the 32-SNP triglyceride GRS with triglyceride levels was stronger than that of the 40-SNP triglyceride GRS (β=0.24 [0.23–0.26], P=1.72×10^-100 versus β=0.20 [0.18–0.22], P=1.86×10^-28, for the 32- and 40-SNP GRS, respectively). We therefore proceeded with the 32-SNP GRS, although we do consider all 40 SNPs in the single SNP analyses. The FI GRS was strongly associated with FI in the combined data set (β=2.33 [1.97–2.67], P=1.34×10^-38). The correlations among the insulin resistance phenotypes, BMI, HDL-C, and WHR are shown in Table II in the Data Supplement. Finally, we find that the triglyceride GRS is not significantly associated with HOMA-IR (β=−0.004 [−0.022, −0.013], P=0.62) or with FI (β=−0.001 [−0.019, −0.016], P=0.89), in a model including age, sex, and study as covariates.

The results of the main effect models of age, sex, BMI, WHR, HDL, triglyceride GRS and each of: FI, FG, and HOMA-IR, with triglyceride levels as the outcome are shown in Table III in the Data Supplement. Table 2 presents the results of the interaction of each of 4 phenotypes with the triglyceride GRS on triglyceride levels in all 3 studies and in the combined data set. In all data sets, we find consistently positive interaction coefficients of all 4 phenotypes with the triglyceride GRS, independently of WHR (for non-WHR outcome phenotypes), BMI, and HDL-C. On the basis of the interaction coefficients, the interaction seems to be stronger for HOMA-IR and FI than for FG (Table 2). The strength of the interaction seems to be smaller in MESA, possibly because of the smaller sample size. Adjustment for relatedness in FHS resulted in slightly attenuated interactions, perhaps because of a reduced sample size (184 individuals without pedigree information). Including only age and sex as covariates, or including age-squared as an additional covariate produced essentially identical results. Using the 40-SNP triglyceride GRS, instead of the 32-SNP GRS, resulted in somewhat attenuated results (β_{interaction} =0.027, P_{interaction} =1.12×10^{-4} for HOMA-IR and β_{interaction} =0.026, P_{interaction} =2.16×10^{-4} for FI). Figure 1 shows the association of the triglyceride GRS with triglyceride in 3 strata (tertiles) of each respective phenotype. The association of the triglyceride GRS with triglyceride was stronger among those individuals with greater insulin resistance, as assessed by HOMA-IR or FI (Figure 1). For example, the association of the triglyceride GRS with triglyceride among those in the highest tertile of HOMA-IR (β=0.24, P=5.6×10^{-22}) was >60% stronger than among those in the lowest tertile of HOMA-IR (β=0.14, P=4.8×10^{-16}). There was no single SNP that drove this interaction, as none reached statistical significance (with same direction of coefficient of interaction) after correction for 40 tests (Figure 2; Table I in the Data Supplement). However, we observed nominally significant interactions for SNPs in/near GCKR, CILP2, and IRS1, and thus these may be strong contributors to the overall GRS trend of interaction with insulin resistance measures. SNPs that exhibited a trend of interaction in the opposite direction (association of SNP with triglyceride levels weaker in the context of insulin resistance) include those near PIVG-NR0B2 (P_{interaction} =6.34×10^{-4}) and LRPAP1 (Figure 2; Table I in the Data Supplement). Although the interaction of the PIVG-NR0B2 SNP with FI was statistically significant after correction for multiple testing, the direction of interaction was opposite to the direction observed for the triglyceride GRS with FI. Among the SNPs found to show at least a nominally significant trend of interaction with the triglyceride GRS, both LRPAP1 and PIVG-NR0B2 were identified in the most recent large-scale meta-analysis.

We did not find a significant interaction of the triglyceride GRS with the FI GRS on triglyceride level.
β interaction = −0.005 and P interaction = 0.59). However, on running pairwise SNP–by–SNP interactions of the individual triglyceride SNPs with the individual FI SNPs, we found a statistically significant interaction of rs4722551 (MIR148A) with rs4865796 (ARL15), whereby the association of rs4722551 with triglyceride levels is accentuated among those individuals with the FI-increasing allele (A) at rs4865796. MIR148A was identified in the most recent large-scale meta-analysis of lipid levels. As shown in Figure 3, the same interaction trend was observed in all 3 studies (ARIC: P interaction = 0.003, FHS: P interaction = 0.02, and MESA: P interaction = 0.22), and achieved statistical significance in the combined data set (P interaction = 4.1×10−5). Adjustment for relatedness in the FHS data set resulted in a slightly higher P value (P = 0.08 within FHS), albeit with a smaller sample size because of 184 individuals without pedigree information. In a model with only age and sex, the P value of this SNP–by–SNP interaction was 3.99×10−4. This attenuation is principally because of the exclusion of HDL-C as a covariate. With age, sex, and HDL-C as covariates, the interaction remains statistically significant (P interaction = 5.06×10−5). In the combined data set, the association of MIR148A with triglyceride levels is stronger in those with the FI-increasing ARL15 genotype (β = 0.043, P = 0.049) compared with those with the FI-decreasing ARL15 genotype (β = −0.13, P = 0.0077).

**Discussion**

Across 3 studies, we find that the association of triglyceride-associated genes with triglyceride levels is stronger among individuals who are insulin resistant, according to FI and HOMA-IR, independently of BMI, WHR, and HDL-C. We also identify the individual SNPs that may be strong contributors to this interaction, as well as an FI SNP–by–triglyceride SNP interaction.

The fact that the 32-SNP GRS explains more of the triglyceride phenotypic variation than the 40-SNP GRS could be related to the fact that the 32-SNP GRS is based on a meta-analysis in which the ARIC and FHS cohorts were included. However, these studies were a relatively smaller part of the most recent meta-analysis (which was based on 37 additional studies typed with the Metabochip).

Using a genetic approach, our results are consistent with previous studies showing that triglyceride levels are increased in the context of insulin resistance. Using a similar approach, Justesen et al also found an interaction of a triglyceride GRS with HOMA-IR on triglyceride levels in the larger of 2 studies that they examined. Although no single SNP seemed to drive the observed GRS interaction in our study, SNPs in/near GCKR, CILP2, and IRS1 stand out as potential drivers. The triglyceride-increasing allele of the GCKR variant was also associated with protection against T2DM in previous studies. These results are consistent with a pattern in which insulin resistance is associated with increased glucose uptake and lipogenesis (ie, de novo lipogenesis) and are consistent with what is known about GCKR, mutations in which can enhance the synthesis of malonyl CoA, a precursor molecule for triglyceride synthesis in the liver. Variants in IRS1 have previously been implicated in the insulin cascade and found to be associated with several cardiometabolic traits. It may be that the association of IRS1 variants with triglyceride levels is mediated by their association with insulin resistance traits. Little is known about CILP2 and how it might relate to lipid levels. Finally, our result suggesting that the association of rs964184 near APOA1-5 with triglyceride levels is accentuated in the context of high-WHR is consistent with previous studies. Another important result is the identification of genes that may have reduced association with triglyceride levels in
the context of insulin resistance. Little is known about how the SNP between PIGV and NR0B2 is related to triglyceride levels. *PIGV* instructs the synthesis of a glycolipid molecule called glycosyl phosphosphatidyl inositol mannosyltransferase, which is known to anchor various proteins on the surface of the cell. NR0B2 (also known as SHP1) regulates diverse biological pathways inside the liver, and mutations in it can alter hepatic cholesterol and triglyceride metabolism. *LRPAP1* codes for the low-density lipoprotein receptor–related protein associated protein 1, which is known to influence cholesterol homeostasis.

Although we did not find an interaction of the triglyceride GRS with the FI GRS, we did identify an interaction of a triglyceride SNP with an FI SNP, which was consistent across all the 3 studies. This interaction involves a triglyceride-associated SNP near *MIR148A* and an FI-associated SNP in *ARL15*. *ARL15* has previously been found to be associated with adiponectin levels, a hormone secreted by adipose tissue and potentially involved in the regulation of glycemic and lipid levels. *MIR148A* has previously been found to be associated with HDL-C. This potentially reinforces the justification for including HDL-C as a covariate in the interaction analysis, particularly for interactions involving SNPs that are also associated with HDL-C. The triglyceride-associated SNP is located near *MIR148A*, which encodes miRNA-148A, a noncoding RNA, which suppresses target mRNAs. miRNA-148A has previously been found to be upregulated in adipogenesis, but downregulated within obese adipocytes, and has been identified in a

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**Figure 2.** Interaction of each triglyceride (TG)-associated single-nucleotide polymorphisms with each corresponding phenotype on TG levels in the combined data set. Interactions with negative coefficients indicate that the association of the TG-increasing allele with TG is weaker in the presence of higher values of the respective phenotype.
Our study is strengthened by the use of multiple phenotypes and genotypes, which are indicative of insulin resistance and the use of 3 datasets to confirm our findings. A limitation of our study is that we are using imperfect sur-
tance and the use of 3 datasets to confirm our findings. A

types and genotypes, which are indicative of insulin resis-

large-scale genome-wide association studies meta-analysis

Figure 3. Association of single-nucleotide polymorphisms
(SNPs) rs4722551 (MIR148A) with triglyceride (TG) levels within 3
genotype strata of SNP rs4865796 (ARL15) in each of 3 studies and
in the combined data set. Error bars represent SEs around the

\( \beta \) coefficients. Models include age, sex, body mass index,
wast/hip ratio, high-density lipoprotein cholesterol, and study, as
covariates. ARIC indicates Atherosclerosis Risk in Communities;

FHS, Framingham Heart Study; and MESA, Multi-Ethnic Study of

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Disclosures

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Clinical Perspective

Insulin resistance (IR) is a central and early feature of metabolic and cardiovascular disease. The molecular pathways that link IR and lipid levels are incompletely characterized at the level of genetic sequence variation. This study builds on previous studies showing a seemingly paradoxical inverse association of triglyceride-increasing alleles with type 2 diabetes mellitus risk, potentially implicating de novo lipogenesis as one responsible mechanism. Because de novo lipogenesis is upregulated in the context of IR, we sought to determine if genetic risk for elevated plasma triglyceride is accentuated in the context of IR (phenotypically and genetically assessed). We examined the interaction of a triglyceride genetic risk score with IR on triglyceride levels across 3 cohorts (total n=12,487). We find that the association of the triglyceride genetic risk score with triglyceride levels is >60% stronger among those in the highest tertile of IR compared with those in the lowest tertile. The main drivers of this pattern seem to include GCKR, CILP2, and IRS1. We also find a statistically significant single-nucleotide polymorphism (SNP)–by–SNP interaction involving a triglyceride-associated SNP near MIR148A, and a fasting insulin–associated SNP in ARL15. Our study sheds light from a genetic perspective on the interplay of lipid and glycemic traits, reveals specific genetic variants that may be major players in this interplay, and identifies a replicated SNP–by–SNP interaction. These findings may pave the way toward identifying novel pathways in cardiometabolic disease and better characterizing currently identified pathways and mechanisms. Improved risk prediction, targeted therapeutics, and prevention strategies may subsequently be realized.