Adiposity significantly modifies genetic risk for dyslipidemia

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Abstract Recent genome-wide association studies have identified multiple loci robustly associated with plasma lipids, which also contribute to extreme lipid phenotypes. However, these common genetic variants explain <12% of variation in lipid traits. Adiposity is also an important determinant of plasma lipoproteins, particularly plasma TGs and HDL cholesterol (HDLc) concentrations. Thus, interactions between genes and clinical phenotypes may contribute to this unexplained heritability. We have applied a weighted genetic risk score (GRS) for both plasma TGs and HDLc in two large cohorts at the extremes of BMI. Both BMI and GRS were strongly associated with these lipid traits. A significant interaction between obese/lean status and GRS was noted for each of TG ($P_{\text{Interaction}} = 2.87 \times 10^{-4}$) and HDLc ($P_{\text{Interaction}} = 1.05 \times 10^{-3}$). These interactions were largely driven by SNPs tagging APOA5, glucokinase receptor (GCKR), and PLTP for TG, and cholesteryl ester transfer protein (CETP), GaINAc-transferase (GaINAcT), endothelial lipase (LIPG), and phospholipid transfer protein (PLTP) for HDLc. In contrast, the GRS$_{\text{LDL}}$ × adiposity interaction was not significant. Sexual dimorphism was evident for the GRS$_{\text{HDL}}$ on HDLc in obese ($P_{\text{Interaction}} = 0.016$) but not lean subjects. SNP by BMI interactions may provide biological insight into specific genetic associations and missing heritability.—Cole, C. B., M. Nikpay, P. Lau, A. F. R. Stewart, R. W. Davies, G. A. Wells, R. Dent, and R. McPherson. Adiposity significantly modifies genetic risk for dyslipidemia. J. Lipid Res. 2014. 55: 2416–2422.

Supplementary key words obesity • genetic risk score • lipoproteins • single nucleotide polymorphism • statistical interaction

Recent genome-wide association studies (GWASs) have identified multiple genetic variants robustly associated with plasma lipid traits. The Global Lipids Consortium reported 157 significant loci ($P < 5 \times 10^{-8}$) (1, 2). Many are novel, and several encompass genes not previously implicated in plasma lipid metabolism. Furthermore, these loci were shown to contribute not only to general variation in plasma lipids, but also to extreme lipid phenotypes (3). Notably, for TGs, individuals in the top quartile of the TG risk score were 44 times more likely to have hypertriglyceridermia as compared with individuals in the bottom quartile ($P = 4 \times 10^{-28}$). For HDL cholesterol (HDLc), individuals in the top quartile of the risk score were four times more likely to have high HDLc as compared with those in the bottom quartile (1).

Although family-based association studies indicate that 40% to 60% of variation in plasma TG and HDLc is genetically based (4, 5), the identified loci explain <12% of variation in each of these lipid traits (1). Environmental and clinical factors including BMI, physical activity, and alcohol intake are also important determinants of plasma TG and HDLc (6).

Thus, interactions between genetic risk factors and clinical phenotypes may account for some of the unexplained heritability of plasma lipid traits. Here we have examined whether the effect of a weighted genetic risk score (GRS) on each of TG and HDLc is modified by adiposity, as assessed by BMI. This study provides biological insight into specific genetic associations and may aid in the identification of dyslipidemic subjects for whom weight loss is likely to be an important intervention.

Abbreviations: CAD-C, coronary artery disease controls; CETP, cholesteryl ester transfer protein; CI, confidence interval; CITTED2, Cbph/p300-interacting transactivator, with Glu/Asp-rich carboxy-terminal domain, 2; FDR, false discovery rate; GaINAcT, GaINAc-transferase; GCK, glucokinase; GCKR, glucokinase receptor; GRS, genetic risk score; GWAS, genome-wide association study; HDLc, HDL cholesterol; LDLc, LDL cholesterol; LIPG, endothelial lipase; OBLE, obese versus lean study; PLTP, phospholipid transfer protein; QC, quality control.

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Study subjects

Subjects with a BMI \(>30 \text{ kg/m}^2\) were defined as obese, those with a BMI \(<23 \text{ kg/m}^2\) as lean, and intermediate subjects (30 kg/m\(^2\) \(>\) 23 kg/m\(^2\)) as normal range. The BMI cutoff of \(<23\) for the lean subgroup is below the 25th percentile for the majority of individuals studied. Two cohorts were studied.

Obese versus lean. Obese, unrelated subjects of strictly European ancestry were recruited from the University of Ottawa Weight Management Clinic. Obese individuals displayed a BMI of \(>35 \text{ kg/m}^2\) and a history of at least 10 years of adult obesity with no medical or psychiatric predisposing factors. Unrelated lean subjects were recruited from the Ottawa community. These healthy individuals had a lifelong BMI of less than the 25th percentile for sex and age, and no medical or psychiatric conditions affecting body weight (7, 8). Body weight was measured using a Tanita electronic scale to the nearest 0.3 kg. BMI was calculated as weight in kilograms divided by height in meters squared (kg/m\(^2\)). Height was measured to the nearest 0.5 cm. Plasma lipid fractions were measured using standard procedures. For coronary artery disease controls (CAD-C) subjects on lipid modifying medication, written documentation of pretreatment plasma lipids was obtained from the primary care physician and used for these analyses. These data were not available for 6.4% of the CAD-C subjects, none of whom were treated with a fibrate or niacin. In the obese versus lean (OBLE) cohort, 2.6% of lean and 14.8% of obese subjects were on low- to moderate-dose statin therapy, not expected to have major effects on TG or HDLc. The study was approved by the Human Ethics Experimentation Committees of the University of Ottawa Heart Institute and the Ottawa Hospital and written informed consent was obtained from all subjects.

CAD-C. Details of the CAD-C cohorts have been previously described (9). Briefly, CAD-C included healthy controls recruited as part of the Ottawa Heart Genomics Study in collaboration with the Cleveland Clinic Gene Bank (OHGS_A and OHGS_CCGB_B). These subsets were combined together to form a single CAD-C sample. Subjects were collected under human research protocols approved by their respective committees.

Genotyping and imputation

SNP genotyping of the OBLE and CAD-C cohorts was performed on Affymetrix 6.0 or 500K Arrays at the University of Ottawa Heart Institute using the standard protocol recommended by the manufacturer and processed as described (10, 11). Imputation was performed using IMPUTE2 and the August 2009 1000 Genomes European reference panel (12). After imputation, \(~5.5\) M SNPs passed post-quality control (QC) measures (info >0.5, Hardy Weinberg Equilibrium >1e-6, missing <10%).

Selection of GWAS SNPs

To create weighted GRSs for TG (GRSTG), and HDLc (GRSHLDLc), we applied the findings of the Global Lipids Consortium 2010 study, which performed a fixed-effects meta-analysis on 46 separate GWASs comprising \(>100,000\) individuals of European descent at a total of \(~2.6\) million imputed or directly genotyped (1). Because the Global Lipids SNPs were identified in populations separate from those being considered here, we have avoided the bias inherent in performing discovery and effect size estimation in the same data set.

RESULTS

The general characteristics of obese and lean subjects in each of the two main cohorts are shown in Table 1. Within the OBLE and CAD-C cohorts, subjects were well matched for age and sex. The OBLE cohort was younger and exhibited greater extremes of BMI [mean 43.1 ± 0.3 (obese); 20.3 ± 0.1 kg/m\(^2\) (lean)] as compared with the CAD-C group [mean BMI 34.6 ± 0.2 (obese); 21.3 ± 0.1 kg/m\(^2\) (lean)]. For the entire group, the mean difference in TG for subjects above or below the 50th percentile of the weighted GRSTG was 0.191 mM [95% confidence interval (CI) = 0.140–0.241, \(P = 1.92 \times 10^{-15}\)]. For obese subjects, this difference was 0.325 mM (95% CI = 0.250–0.399, \(P < 2.20 \times 10^{-15}\)) and for lean subjects 0.114 mM (95% CI = 0.250–0.399, \(P < 2.20 \times 10^{-16}\)). The mean difference in HDLc for
TABLE 1. Characteristics of the study sample separated by cohort and by trait under study

| Trait | n | Male (%) | Age (years) | BMI (kg/m^2) | Risk Score |
|-------|---|----------|-------------|--------------|------------|
| TG    |   |          |             |              |            |
| Lean  | 1,784 | 34.1 | 45.4 ± 0.3 | 31.8 ± 0.3 | −0.198 ± 0.01 |
| Obese | 916   | 28.9 | 46.4 ± 0.4 | 43.1 ± 0.3 | −0.204 ± 0.013 |
| HDL   |   |          |             |              |            |
| Lean  | 1,779 | 34.3 | 45.5 ± 0.3 | 31.7 ± 0.3 | 0.007 ± 0.001 |
| Obese | 911   | 25.1 | 46.4 ± 0.4 | 43.0 ± 0.3 | 0.005 ± 0.002 |
| CAD-C |   |          |             |              |            |
| TG    |   |          |             |              |            |
| Lean  | 2,966 | 49.4 | 75 ± 0.1 | 26.3 ± 0.1 | −0.149 ± 0.006 |
| Obese | 788   | 46.4 | 75.8 ± 0.2 | 21.6 ± 0.1 | −0.142 ± 0.011 |
| Normal| 1,840 | 55.2 | 74.9 ± 0.1 | 26.8 ± 0.1 | −0.153 ± 0.007 |
| HDL   |   |          |             |              |            |
| Lean  | 2,937 | 49.3 | 74.9 ± 0.1 | 26.3 ± 0.1 | −0.006 ± 0.001 |
| Obese | 596   | 48.2 | 76.1 ± 0.2 | 21.1 ± 0.1 | −0.006 ± 0.002 |
| Normal| 498   | 32.6 | 73.9 ± 0.2 | 33.4 ± 0.1 | −0.005 ± 0.002 |

Values represent mean ± standard deviation, unless otherwise indicated. Lean: BMI <23 kg/m^2 and less than 25th percentile. Obese: BMI >30 kg/m^2 for >10 years. Normal: 23 kg/m^2 ≤ BMI ≤ 30 kg/m^2. Risk score corresponds to the sum of the effect size per risk gene multiplied by the effect size of that risk gene, divided by the total number of risk genes. Data are provided as mean ± standard deviation. See supplementary Table I for further details.

TABLE 2. Associations of GRS with adjusted lipid trait stratified by adiposity

| Trait | n | Male (%) | Age (years) | BMI (kg/m^2) | Risk Score |
|-------|---|----------|-------------|--------------|------------|
| TG    |   |          |             |              |            |
| Obese | 1,222 | 34.8 (0.053) | 8.98E−19 | 0.0614 |            |
| Lean  | 1,376 | 1.466 (0.0165) | 2.49E−18 | 0.0533 |            |
| HDL   |   |          |             |              |            |
| Obese | 1,656 | 34.1 (0.034) | 1.52E−14 | 0.0345 | 0.000287 |
| Lean  | 1,464 | 2.347 (0.209) | 3.41E−28 | 0.0790 | 0.00105 |

Number of nonmissing individuals with complete information included in analysis. β coefficient for regression, measured in mM.

demonstrating significant interactions for obese/lean status × GRS_{HDL} (P_{interaction} = 1.05 × 10^{-3}) (Fig. 2). For GRS_{LDL} in the obese population, β = 0.434 mM (SE = 0.0831, P = 2.14 × 10^{-7}), similar to the lean population where β = 0.390 mM (SE = 0.0715, P = 5.63 × 10^{-6}). As expected, no significant interaction between GRS_{LDL} and obese/lean status was found (P_{interaction} = 0.689). Subjects with a BMI in the normal range (23 kg/m^2 < BMI < 30 kg/m^2) exhibited a value between the lean and obese for TG, β = 0.354 mM (SE = 0.0289, P = 4.68 × 10^{-16}); for HDLc, β = 1.91 mM (SE = 0.126, P = 2.16 × 10^{-30}); but not for LDL, β = 0.464 mM (SE = 0.0473, P = 1.54 × 10^{-22}). Subjects with a BMI in the normal range (23 kg/m^2 < BMI < 30 kg/m^2) exhibited a value between the lean and obese for TG, β = 0.354 mM (SE = 0.0289, P = 4.68 × 10^{-16}); for HDLc, β = 1.91 mM (SE = 0.126, P = 2.16 × 10^{-30}); but not for LDL, β = 0.464 (SE = 0.0473, P = 1.54 × 10^{-22}).
SNP (i) divided by the number of SNPs analyzed (number of tests performed) multiplied by the FDR was determined to be the cutoff at which results were classified as significant (16). Further details regarding SNP × obese/lean status analyses are provided in supplementary Table II. To test whether these SNPs were the major contributors to the overall obese/lean status × GRS interaction, a new score was constructed for each group omitting these SNPs. As expected, the interaction term was no longer significant (TG: $P_{\text{Interaction}} = 0.196$; HDLc: $P_{\text{Interaction}} = 0.321$).

Sex × lipid trait interactions

Next, we investigated whether GRS effects differed by sex. Of note, sex did not significantly influence the effect of the GRS on any trait in the whole population (TG: $P_{\text{Interaction}} = 0.0925$; HDLc: $P_{\text{Interaction}} = 0.0868$; LDL: $P_{\text{Interaction}} = 0.189$). However, for GRS$_{\text{HDLc}}$ on HDLc, there was a significant interaction with sex in the obese ($P_{\text{Interaction}} = 0.016$) but not the lean ($P_{\text{Interaction}} = 0.369$) population. A sex dimorphic effect by obese/lean stratification was not found for the other lipid traits. Further analysis of individual SNPs failed to identify significant interaction terms in the whole population.

Because obesity status significantly influenced the clinical expression of these lipid trait loci, we determined the explained variance ($R^2$) of the GRS$_{\text{TG}}$ and GRS$_{\text{HDLc}}$ in obese versus lean subjects. For GRS$_{\text{TG}}$ on TG, $R^2 = 0.0614$ for obese versus $R^2 = 0.0345$ for lean subjects, a 2-fold difference. An opposite trend was observed for GRS$_{\text{HDLc}}$ (based on HDLc-raising alleles) on HDLc, $R^2 = 0.0790$ for lean versus $R^2 = 0.0533$ for obese. In contrast, for the GRS$_{\text{LDLc}}$ on LDLc, explained variance was only slightly higher in the obese ($R^2 = 0.0215$) versus lean ($R^2 = 0.0172$) populations.

We next examined the individual SNPs included in the GRS$_{\text{TG}}$ and GRS$_{\text{HDLc}}$. Three TG SNPs (APOA5, GCKR, and LPL) and four HDLc SNPs (CEP, LPG, GALNT2, and PLTP) were found to have a significant obese/lean status × SNP effect interaction term at a false discovery rate (FDR) of 20% (Table 3). LPL and APOA5 achieved a 10% FDR for TG, and CETP, GALNT2, and LPG reached a 10% FDR for HDLc. However, at a 5% FDR, only LPL and CETP were significant. Statistical correction for multiple testing was achieved by ordering each tested SNP from least to greatest $P_{\text{Interaction}}$ value. The largest interaction term that was less than the $P_{\text{FDR}}$ i.e., the ratio of the position of the SNP (i) divided by the number of SNPs analyzed (number of tests performed) multiplied by the FDR was determined to be the cutoff at which results were classified as significant (16). Further details regarding SNP × obese/lean status analyses are provided in supplementary Table II. To test whether these SNPs were the major contributors to the overall obese/lean status × GRS interaction, a new score was constructed for each group omitting these SNPs. As expected, the interaction term was no longer significant (TG: $P_{\text{Interaction}} = 0.196$; HDLc: $P_{\text{Interaction}} = 0.321$).

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**DISCUSSION**

Lifestyle and clinical factors may modify genetic risk. For example, the effect of a GRS on BMI was found to be significantly attenuated in physically active versus sedentary individuals (17). To explore the effects of adiposity on genetic risk for dyslipidemia, we have utilized a GRS constructed from loci previously reported by the Global Lipids Consortium. We demonstrate that obesity status significantly influences the genetic risk for dyslipidemia. However, after correction for multiple testing, some loci were only nominally significant (FDR = 15%) (Table 4). More complete SNP × sex interaction data may be found in supplementary Table III.

**TABLE 3. Individual loci that exert differing effects in obese versus lean subjects**

| Locus   | Lead SNP    | Allele* | Trait | n | β (SE) | P      | n | β (SE) | P      | n | β (SE) | P      | n | β (SE) | P      |
|---------|-------------|---------|-------|---|--------|--------|---|--------|--------|---|--------|--------|---|--------|--------|
| LPL     | rs12678919  | G       | TG    | 945 | -0.148 (0.03) | 4.03E-06 | 932 | -0.050 (0.03) | 4.03E-06 | 1,877 | -0.21 (0.06) | 6.99E-04 | 0.01 |
| APOA5   | rs964184    | G       | TG    | 1,078 | 0.159 (0.03) | 1.31E-07 | 1,282 | 0.14 (0.03) | 1.91E-07 | 2,415 | 0.15 (0.06) | 8.87E-03 | 0.02 |
| GCKR    | rs1260326   | T       | TG    | 1,189 | 0.0932 (0.03) | 1.21E-03 | 1,569 | 0.067 (0.02) | 6.84E-03 | 2,758 | 0.12 (0.05) | 2.82E-02 | 0.03 |
| CETP    | rs3764261   | A       | HDL   | 1,083 | 0.132 (0.03) | 1.67E-06 | 1,282 | 0.189 (0.03) | 3.15E-13 | 2,415 | 0.21 (0.05) | 1.14E-05 | 0.005882 |
| GALNT2  | rs4846914   | G       | HDL   | 1,212 | -0.065 (0.03) | 1.24E-02 | 1,463 | -0.092 (0.02) | 9.39E-01 | 2,829 | -0.13 (0.05) | 3.03E-03 | 0.017647 |
| LIPG    | rs7241918   | G       | HDL   | 1,061 | -0.004 (0.03) | 8.96E-01 | 1,178 | -0.102 (0.03) | 1.35E-04 | 2,329 | 0.13 (0.05) | 7.00E-03 | 0.017647 |
| PLTP    | rs6065906   | C       | HDL   | 1,184 | -0.034 (0.03) | 2.01E-01 | 1,435 | -0.107 (0.02) | 1.19E-05 | 2,769 | 0.10 (0.04) | 2.08E-02 | 0.023529 |

*Active allele analyzed.

Number of nonmissing individuals with complete information used in analysis.

β coefficient for regression; measured in mM (standard error).

FDR of 20% displayed. All achieved FDR <20%; APOA5, GALNT2, and LIPG achieved FDR <10%; LPL and CETP achieved FDR <5%.
Table 4. Individual SNPs with suggestive evidence of sexual dimorphism

| Locus | Lead SNP | Allele | Pop | n' | β (SE) | P   | n | β (SE) | P   | PInteraction | PInmt |
|-------|----------|--------|-----|----|--------|-----|---|--------|-----|-------------|-------|
| GALNT2 | rs4846914 | G       | OB  | 405 | 0.060 (0.05) | 2.15E-01 | 807 | -0.12 (0.03) | 3.97E-04 | 1.212 | 0.14 (0.04) | 2.09E-03 | 4.84E-03 |
| CITED2 | rs605066  | C       | LE  | 515 | 0.694 (0.29) | 1.75E-02 | 894 | -0.058 (0.03) | 7.77E-02 | 1.409 | 0.12 (0.04) | 4.57E-03 | 4.84E-03 |

*Active allele analyzed.

**Population where loci are active.

†Number of nonmissing individuals with complete information used in analysis.

β coefficient for regression; measured in mM (standard error).

FDR of 15% displayed. GALNT2 is significant at <10% FDR.

Although we lack the statistical power necessary to detect the individual effects of all loci, we identified seven novel loci not previously reported to have obesity-related dimorphic effects. SNPs tagging APOA5 (PInteraction = 8.87 × 10⁻⁵), GCKR (PInteraction = 2.82 × 10⁻³), and LPL (PInteraction = 6.69 × 10⁻⁴) showed interaction with obese/lean status for TG. These encompass genes encoding proteins altering both hepatic TG synthesis and peripheral lipolysis. The GCKR gene product, the glucokinase regulatory protein, regulates glucokinase (GCK) activity competitively with respect to the substrate glucose, inhibiting GCK activity. Hepatic GCK activity enhances glycolytic flux, promoting hepatic glucose metabolism and increasing malonyl CoA availability, a major substrate for de novo hepatic lipogenesis (18). LPL and APOA5 encode major determinants of peripheral lipolysis of TG-rich lipoproteins, LPL and ApoA5, the latter a regulator of LPL activity (19). The effect sizes of the previously discussed TG loci were among the highest in this study (APOA5b = 16.95, GCKRb = 8.76, and LPl = -13.64) and not surprisingly were responsible for the significant obese/lean status × GRS interaction. Consistently, in a Filipino population the APOA5 effect on plasma TG levels was found to be modified by waist circumference (20), another measure of adiposity.

For HDLc, interactions were noted for SNPs tagging CETP (PInteraction = 1.14 × 10⁻⁵), LIPG (PInteraction = 7.00 × 10⁻⁵), GALNT2 (PInteraction = 3.03 × 10⁻³), and PLTP (PInteraction = 2.08 × 10⁻³). The roles of CETP, LIPG, and PLTP in HDL remodeling in the intravascular space are well known. GALNT2 encodes GalNAc-transferase believed to play a critical role in O-glycosylation of proteins involved in lipid metabolism, including angiopoietin-like 3 (21). In the mouse, altered hepatic GALNT2 expression significantly modifies circulating HDLc levels (1). Although these HDLc loci exhibited lower effect sizes (CETPb = 3.39, LIPGb = -1.31, PLTPb = -0.93, and GALNT2b = -0.61) as compared with the top TG SNPs, they were similarly responsible for the significant GRSHDL × obese/lean status interaction term. In contrast, no significant interaction was found for GRSHDL × obese/lean status.

In a second stage, we performed a sex-stratified analysis. The effect of neither weighted GRS TG nor GRS HDLc was found to be significantly different for males versus females for the population as a whole. Importantly, sexual dimorphism for genetic effects on HDLc was entirely driven by the obese subjects (PInteraction = 0.016) and was not evident in the lean (PInteraction = 0.914) or all (PInteraction = 0.0868).
groups. Obese men showed an attenuated increase in HDLc in response to GRS_HDLc, as compared with women (Fig. 3). Loci in each subpopulation (CITED2 for obese and GALNT2 for lean) were found to be dimorphic (Table 4). However, after correction for multiple testing, these remained only nominally significant (FDR < 15%), thus requiring confirmation in additional populations.

In summary, we have created weighted GRSs for each of TG and HDLc based on loci identified by the Global Lipids Consortium and tested effects in separate large, well-defined obese and lean populations; thus, our results are without discovery bias. Neither GRS_TG nor GRS_HDLc showed an association with adiposity (BMI) per se. Here we demonstrate convincing gene-adiposity trait interactions. Notably, lean subjects have an attenuated response to HDLc-raising alleles, as compared with obese subjects. These effects are mainly driven by SNPs tagging APOA5, GCKR, and LPL for TG, and CETP, LIPC, GALNT2, and PLTP for HDLc. We also report sexual dimorphism for genetic effects on HDLc that is confined to the obese group of subjects. These findings demonstrate that obese individuals are more susceptible to genetic risk for dyslipidemia. SNP by BMI interactions may provide biological insight into specific genetic associations and missing heritability.

REFERENCES

1. Teslovich, T. M., K. Musunuru, A. V. Smith, A. C. Edmondson, I. M. Stylianou, M. Koseki, J. P. Pirruccello, S. Ripatti, D. I. Chamman, C. J. Willer, et al. 2010. Biological, clinical and population relevance of 95 loci for blood lipids. Nature. 466: 707–713.

2. Willer, C. J., E. M. Schmidt, S. Sengupta, G. M. Peloso, S. Gustafsson, S. Kanoni, A. Ganna, J. Chen, M. L. Buchkovich, S. Mora, et al. 2013. Discovery and refinement of loci associated with lipid levels. Nat. Genet. 45: 1278–1283.

3. Johansen, C., T. J. Wang, M. B. Lanktree, A. D. McIntyre, M. R. Ban, R. A. Martins, B. A. Kennedy, R. G. Hassel, M. E. Visser, S. M. Schwartz, et al. 2011. An increased burden of common and rare lipid-associated risk alleles contributes to the phenotypic spectrum of hypertriglyceridemia. Arterioscler. Thromb. Vasc. Biol. 31: 1916–1926.

4. Namboodiri, K. K., E. B. Kaplan, I. Heuch, R. C. Elston, P. F. Green, D. C. Rao, P. Laskarzewski, C. J. Glueck, and B. M. Rifkind. 1985. The Collaborative Lipid Research Clinics Family Study: biological and cultural determinants of familial resemblance for plasma lipids and lipoproteins. Genet. Epidemiol. 2: 227–254.

5. Yu, Y., D. F. Wyszynski, D. M. Waterworth, S. D. Wilton, P. J. Barter, Y. A. Kesaniemi, R. W. Mahley, R. McPherson, G. Waerber, T. P. Bersot, et al. 2005. Multiple QTLs influencing triglyceride and HDL and total cholesterol levels identified in families with atherogenic dyslipidemia. J. Lipid Res. 46: 2202–2213.

6. Howard, B. V., G. Ruotolo, and D. C. Robbins. 2003. Obesity and dyslipidemia. Endocrino. Metab. Clin. North Am. 32: 855–867.

7. Ahituv, N., K. Kavaslar, W. Schackwitz, A. Ustaszewska, J. Martin, S. Hebert, H. Doelle, B. Ersoy, G. Kryukov, S. Schmidt, et al. 2007. Medical sequencing at the extremes of human body mass. Am. J. Hum. Genet. 80: 779–791.

8. Davies, R. W., P. Lau, T. Naing, M. Nikpay, H. Doelle, M. E. Harper, R. Dent, and R. McPherson. 2013. A 680 kb duplication at the FTO locus in a kindred with obesity and a distinct body fat distribution. Eur. J. Hum. Genet. 21: 1417–1422.

9. Davies, R. W., G. A. Wells, A. F. Stewart, J. Erdmann, S. H. Shah, J. F. Ferguson, A. S. Hall, S. St. S. Szajed, M. S. Burnett, S. E. Epstein, et al. 2012. A genome-wide association study for coronary artery disease identifies a novel susceptibility locus in the major histocompatibility complex. Circ. Cardiovasc. Genet. 5: 217–225.

10. Dandona, S. A., A. F. Stewart, L. Chen, K. Williams, D. So, E. O’Brien, C. Glover, M. Lemay, O. Assogba, L. Vo, et al. 2010. Gene dosage of the common variant 9p21 predicts severity of coronary artery disease. J. Am. Coll. Cardiol. 56: 479–486.

11. Schunkert, H., I. R. Konig, S. Kathiresan, M. P. Reilly, T. L. Assimes, H. Holm, M. Preuss, A. F. Stewart, M. Barbalic, C. Gieger, et al. 2011. Large-scale association analysis identifies 13 new susceptibility loci for coronary artery disease. Nat. Genet. 43: 333–338.

12. Howie, B. N., P. Donnelly, and J. Marchini. 2009. A flexible and accurate genotype imputation method for the next generation of genome-wide association studies. PLoS Genet. 5: e1000529.

13. Dudbridge, F. 2013. Power and predictive accuracy of polygenic risk scores. PLoS Genet. 9: e1003548.

14. Purcell, S., B. Neale, K. Todd-Brown, L. Thomas, M. A. Ferreira, D. Bender, J. Maller, P. Sklar, P. I. de Bakker, M. J. Daly, et al. 2007. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am. J. Hum. Genet. 81: 559–575.

15. Davies, R. W., S. Dandona, A. F. Stewart, L. Chen, S. G. Ellis, W. H. Tang, S. L. Hazen, R. Roberts, R. McPherson, and G. A. Wells. 2010. Improved prediction of cardiovascular disease based on a panel of SNPs identified through genome-wide association studies. Circ. Cardiovasc. Genet. 3: 468–474.

16. Benjamini, Y., and Y. Hochberg. 1995. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. R. Stat. Soc. B. 57: 289–300.

17. Li, S. J., H. Zhao, J. Luan, U. Ekelund, R. N. Laben, K. T. Khaw, N. J. Wareham, and R. J. Loos. 2010. Physical activity attenuates the genetic predisposition to obesity in 20,000 men and women from EPIC-Norfolk prospective population study. PLoS Med. 7: e1000332.

18. Beer, N. L., N. D. Tribble, J. L. McCulloch, C. Roos, R. P. Johnson, M. Ortho-Melander, and A. L. Glyn. 2009. The P446L variant in GCRK associated with fasting plasma glucose and triglyceride levels exerts its effect through increased glucokinase activity in liver. Hum. Mol. Genet. 18: 4081–4088.

19. Grosskopf, I., N. Barouki, S. J. Lee, Y. Kamari, D. Harats, E. M. Rubin, L. A. Pennacchio, and A. D. Cooper. 2005. Apolipoprotein A-V deficiency results in marked hypertriglyceridemia attributable to decreased lipolysis of triglyceride-rich lipoproteins and removal of their remnants. Arterioscler. Thromb. Vasc. Biol. 25: 2573–2579.

20. Wu, Y., A. F. Marvelle, J. Li, D. C. Croteau-Chonka, A. B. Feranil, C. W. Kuzawa, Y. Li, L. S. Adair, and K. L. Mohlke. 2013. Genetic association with lipids in Filipinos: waist circumference modifies an APOA5 effect on triglyceride levels. J. Lipid Res. 54: 3198–3205.

21. Schiodtager, K. T., M. B. Vester-Chrestensen, E. P. Bennett, S. B. Levery, T. Schwinietz, W. Yin, O. Blixt, and H. Clausen. 2010. O-glycosylation modulates proprotein convertase activation of angiotensin-I-like protein 3: possible role of polypeptide GalNAc-transferase-2 in regulation of concentrations of plasma lipids. J. Biol. Chem. 285: 36293–36303.