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Editorial

Gene and Metabolic Environment Interactions in Obesity and Diabetes

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EDITORIAL

We are thankful to Dr. Masayoshi Yamaguchi for his keen interest in our previous study in the field of Obesity and Diabetic genetic-diet interactions research.

Since 2007, genome-wide association studies (GWAS) have contributed to a major leap forward in understanding the genetic basis of obesity and diabetes [1–4]. To date, 37 genetic loci associated with obesity or body mass index (BMI) have been identified through these GWAS which were predominantly in populations of European ancestry. We conducted a meta-analysis of associations between BMI and approximately 2.4 million single-nucleotide polymorphism (SNPs) in 27,75 East Asians, including seven loci previously identified by studies conducted among European-ancestry populations (FTO, SEC6B, MC4R, GIPR/QPCTL, ADCY3/RBJ BDNF, and MAP2K5) and three novel loci in or near the CDKAL,PCSK, and GP2 genes [5].

Three additional loci nearly reached the genome-wide significance threshold, including two previously identified loci in the GNPDA2 and TFAP2B genes and a new locus near PAX6, which all had $P<5.0\times0^{-7}$. Of the three previously reported loci at GIPR/QPCTL, ADCY3/RBJ, and MAP2K5), conditional analyses with both SNPs at the same locus included in the same models showed that only the SNPs identified by our study were associated with BMI in East Asian populations. The representative SNP (rs26967) near the newly identified PCSK gene exhibited a significant association (P=0.0058) with BMI in a European population. As expected, the explained variances of the previously reported loci were generally lower in East Asians compared with those in Europeans, while the explained variances for the newly identified loci from this study were generally larger in East Asians than in Europeans. The identification of new loci may shed light on new pathways involved in obesity and demonstrate the value of conducting genetic studies in non-European populations. In addition, fine mapping of multiethnic populations could lead to identification of causal links.

Recent GWAS identified the common genetic variant rs228709 in the gastric inhibitory polypeptide receptor (GIPR) locus that is associated with obesity risk [6], and major allele C, which increases BMI (in kg/m^2), was also reported to be associated with higher fasting glucose but lower 2-h glucose concentrations in a glucose challenge test [7,8]. The direction of the genetic effect is concordant with the function of GIPR signaling [9]. Given the close relation between GIPR signaling and the ingestion of dietary fat, Qibin Qi et al hypothesized that diets that vary in fat content might differentially affect the genetic effect of GIPR on body weight and related metabolic traits [10].

They tested this hypothesis in participants in a 2-y randomized diet-intervention trial (POUNDS LOST) [], in which 8 overweight participants were randomly assigned to of 4 diets with different compositions of macronutrients. They investigated the effect of the newly identified GIPR variant rs228709 on changes in body weight, fasting glucose, and insulin resistance in response to diets that varied in fat content in the intervention.

At 6 month of diet intervention, the T allele of rs228709 was associated with greater weight loss and greater decreases in fasting glucose, fasting insulin and HOMA-IR in participants who were assigned to low-fat diets, whereas there was no significant genotype effect on changes in these traits in the group assigned to the high-fat diet (all P>0.44; P-interaction = 0.08, 0.04, 0.0, and 0.07, respectively). After correction for multiple tests (significant P = 0.008), the genotype effect on changes in fasting glucose remained significant. Sensitivity analysis in white participants showed that the interactions were more evident on changes in insulin and HOMA-IR (P -interaction, 0.008).

Dyslipidemia has been associated with type 2 diabetes [2], and the most common patterns of dyslipidemia in diabetic patients are reduced HDL and elevated TG levels. However, it remains unclear whether low HDL/high TG levels play a causal role in the development of type 2 diabetes [3,4]. Information on the associations of genetic predisposition to dyslipidemia with risk of type 2 diabetes might help clarify the causality. Recently, a meta-analysis of 46 lipid genome-wide association studies comprising 00,000 individuals of European ancestry has established more comprehensive genetic profiles for various blood lipids, including LDL cholesterol, HDL cholesterol, and triglycerides [5].

In the current study, Qibin Qi et al calculated three genotype scores on the basis of well-established SNPs for LDL, HDL and TG, respectively [6]. Genetic predisposition to dyslipidemia was estimated by three genotype scores of lipids (LDL cholesterol, HDL cholesterol, and triglycerides) on the basis of the established

loci for blood lipids. Linear relation analysis indicated that the HDL cholesterol and triglyceride genotype scores, but not the LDL cholesterol genotype score, were linearly related to elevated type 2 diabetes risk. Each point of the HDL cholesterol and triglyceride genotype scores was associated with a 3% (.03[.0 –.04]) and a 2% (.02 [.00 –.04]) increased risk of developing type 2 diabetes, respectively. The ORs were .39 (.7–.65) and .9 (.0–.4) for type 2 diabetes by comparing extreme quartiles of the HDL cholesterol genotype score and triglyceride genotype score, respectively. In conclusion, genetic predisposition to low HDL cholesterol or high triglycerides is related to elevated type 2 diabetes risk.

Emerging evidence has shown that circulating amino acids may play an important role in the pathogenesis of metabolic disorders such as obesity, insulin resistance and type 2 diabetes (T2D) [7,8]. Recently, using metabolomic profiling methods, Wang et al. identified that high levels of circulating branched-chain amino acids (BCAAs) and aromatic amino acids (AAAs) predicted T2D in two prospective cohorts. These circulating amino acids were elevated up to 2 years before the onset of diabetes and associated higher insulin resistance [9].

Interestingly, blood levels of amino acids are partially determined by genetic factors. A recent GWAS found a SNP rs44058 near the PPMKgene (PP2C domain-containing protein phosphatase K) to be associated with higher serum valine levels; and the ratio of BCAA to AAA (Fischer's ratio), which is characteristic of liver fibrosis and may contribute to hepatic encephalopathy [20]. According to the Mendelian randomization principle [2, 22] a genetic variant could be a better marker than biomarkers in causal inference because it is less likely to be affected by confounding and reverse causation [23]. In the present study, we examined the effects of a circulating BCAA to AAA ratio associated genetic variant on changes in weight and insulin resistance in the 2- year Preventing Overweight Using Novel Dietary Strategies (POUNDS LOST) trial, and particularly assessed gene-diet interactions [24].

We genotyped a BCAA/AAA ratio associated variant rs44058 near the PPMK gene in 734 overweight or obese adults who were assigned to one of four diets varying in macronutrient content. At 6 months, dietary fat significantly modified genetic effects on changes in weight, fasting insulin and homeostasis model assessment of insulin resistance (HOMA-IR), after adjustment for the confounders (all P for interaction≤0.006). Further adjustment for weight change did not appreciably change the interactions for fasting insulin and HOMA-IR. In the high-fat diet group, the C allele was related to less weight loss and smaller decreases in serum insulin and HOMA-IR (all P≤0.02 in an additive pattern); while an opposite genotype effect on changes in insulin and HOMA-IR was observed in low-fat diet group (P = 0.02 and 0.04, respectively). At 2 years, the gene–diet interactions remained significant for weight loss (P = 0.008), but became null for changes in serum insulin and HOMA-IR due to weight regain. Above all, individuals carrying the C allele of a BCAA/AAA ratio associated variant rs44058 may benefit less in weight loss and improvement of insulin sensitivity than those without this allele when undertaking an energy-restricted high-fat diet.

Neuropeptide Y gene (NPY) is widely expressed in the peripheral and central nervous systems and is involved in BP regulation [25]. NPY levels are modulated by dietary factors, especially dietary fat [26]. Recently, a functional single nucleotide polymorphism (SNP) in the promoter region of NPY, rs647 (C-399T), was found to be related to risks for early onset atherosclerosis [27] and showed allele-specific effects on NPY gene expression and NPY peptide level [27,28]. However, no study has examined the effect of this functional genotype and its interaction with dietary factors on BP.

We evaluated the potential effect of a functional variant rs647 located in the NPY gene promoter region on the association between 2-year diet intervention and change in multiple BP measures in the randomized Preventing Overweight Using Novel Dietary Strategies Trial [29]. The NPY rs647 was genotyped in 723 obese adults who were randomly assigned to of 4 diets differing in the target percentages of energy derived from fat, protein, and carbohydrate. The changes of BP during 2-year diet intervention were analyzed. In the total participants and participants with hypertension, we observed significant and consistent interactions between rs647 genotype and dietary fat intake on changes in multiple BP phenotypes at 2 years (all P for interactions <0.05). The risk allele (C allele) was associated with a greater reduction of BP phenotypes in response to low-fat diet, whereas an opposite genetic effect was observed in response to high-fat diet. In addition, the C allele was related to greater changes in hypertensive compared with nonhypertensive participants. In conclusion, our data suggest that NPY rs647 may modulate the association between dietary fat intake and BP regulation, and the C allele exerts a long-term beneficial effect on lowering BP in response to low-fat diet in obese and hypertensive subjects.

Some limitations of the study should be addressed. First, HOMA-IR was used as an indicator of insulin resistance instead of a euglycemic hyperinsulinemic clamp. However, the markers included in our study have been tightly related to the clamp and widely used in clinical practice. Second, the results may not be generalized to other ethnic groups since 80% of the participants were whites in the current study. Third, our sample size rendered us insufficient power to test gene-diet interactions for rare variants. Finally, because the majority of the participants in the present study are whites and of a specific body mass index range, the generalizability of our findings to other minority groups or the general population with normal range of body weight needs to be further verified. Further studies in other populations of different ethnicities are needed.

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