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Gene-Diet Interactions in Type 2 Diabetes

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ABSTRACT

The number of type 2 diabetes (T2D) patients has augmented sharply over the past decades and become a major public health threat worldwide. Compelling evidence demonstrates a transition from traditional (principally nutritionally dense) diet to more energy-dense (Western-pattern) diet plays a pivotal role in promoting the epidemic of T2D. With revolutionary advances in genotyping and sequencing methodology, large-scale genome-wide association studies (GWASs) have made great strides in unraveling the genetic basis of T2D, and facilitating efforts to investigate gene-diet interaction. A great group of studies have been performed to assess interactions between genetic factors and dietary factors, mostly focusing on candidate genes and being conducted in small-sized observational settings. Recently, reports from large scale prospective cohorts and randomized clinical trials are emerging. In addition, it remains a major challenge to convert the findings into public health and medical practice.

Keywords: Type 2 diabetes, Gene, Diet, Interaction

Abbreviations: CI: Confidence Interval; GWAS: Genome-Wide Association Study; HR: Hazard Ratio; IGR: Impaired Glucose Regulation; OR: Odds Ratio; SNP: Single Nucleotide Polymorphisms; T2D: Type 2 Diabetes

INTRODUCTION

As one of the leading causes of morbidity and mortality, diabetes has become one of the leading health threats worldwide. Globally, the number of diabetes patients has been predicated to be 552 million by 2030 [1]. Moreover, more than 90% patients are classified as type 2 diabetes (T2D), and insulin resistance and beta cell dysfunction are the major pathophysiologic basis of T2D.

T2D is one of the major metabolic disorders closely related to environment factors, such as lifestyle and diet. A large body of data from epidemiological studies has consistently shown that several dietary factors are linked to risk of T2D. For example, high intakes of trans- and saturated fat, refined grains, red meats or processed meats, fried-foods and sugar-sweetened beverages have been related to increased risk of T2D [2-5], whereas high consumption of whole grains, fruits and vegetables, legumes, nuts, coffee, and moderate alcohol reduced the T2D risk [2,4,6,7]. Particular dietary patterns stated by combinations of different foods and nutrients have also been associated with T2D risk [4,8].

Since 2007, application of genome-wide association studies (GWAS) in population studies has made great breakthrough in uncovering the genetic basis of T2D. *HHEX* and *SLC30A8* were the first GWAS-identified new diabetes loci [9].

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After then, larger-scale meta-analyses of GWAS have identified more T2D-associated loci. The first round of meta-analysis by the Diabetes Genetics Replication and Meta-analysis (DIAGRAM) consortium identified 6 novel loci [10], and the second round meta-analysis [11] identified 12 additional loci. Another including 21 cohort data of European decent GWAS meta-analysis conducted by the Glucose and Insulin-Related Traits Consortium (MAGIC) identified 5 T2D associated loci [12]. To date, around 70 loci have been confirmed as T2D susceptibility loci [13,14].

It has been noted for a long time that response to environmental risk factors and clinical interventions varies considerably between individuals, suggesting that environmental factors, genetic components and their interactions determine an individual's risk for T2D [15,16]. To date, interactions between genetic and environmental factors such as dietary factors are hypothesized to raise T2D risk in a synergistic manner in most cases. Defining the nature of gene-diet interactions that can be translated into the public health setting may help optimize targeting of health interventions. In this article, we focused on describing the latest rationale and evidence concerning the interaction effect of gene and dietary factors on T2D. In addition, we provide an interpretation of current findings and strategies and offer a view for their future translation.

Why Do We Think Gene-Diet Interaction Is Important to Type 2 Diabetes ?

The effects of individual genetic variants are generally modest. The odds ratios (ORs) of each risk allele with target disease usually range from 1.1 to 1.3 [17]. Additionally, when all the identified genetic variants are considered together, they only account for a small proportion of the disease risk, meaning huge 'missing heritability' [18]. It is believed that interactions between the genetic variants and environmental risk factors could explain at least part of the missing heritability [19]. However, most of the previous genetic researches did not consider the potential modification from environmental factors.

A popular yet contentious explanation for why indigenous groups (whose evolution has involved long periods of migrant, hunter-gatherer lifestyles, and frequent famine) are so susceptible to the adverse consequences of industrialized environments is termed as the "thrifty gene hypothesis", first proposed by Neel in 1992 [20], which can explain the rapid increase of diabetes and obesity in modern society. According to this hypothesis, the diabetes or obesity-predisposing genotypes would have been advantageous in the early evolutionary history because these genotypes promote fat deposition in adipocytes, which protect human beings to survive at the period of famine (positive selection). However, such genotypes become disadvantageous in modern society when excessive automation and almost effortless access to energy-dense foods, calorie accumulation and storage and over-nutrition has become popular [20]. If the hypothesis is true, it may provide a judicious model to account for the gene-diet interaction. However, evidence directly supporting the hypothesis is largely lacking. Recently, Ayub et al. [21] tried to test the hypothesis at 65 loci associated with T2D in samples of African, European, and East Asian ancestry. The results failed to demonstrate that positive selection has a powerful effect on driving the prevalence of T2D risk.

Even though, studies attempting to test the gene-environment interaction have provided preliminary evidence to support that such interactions between the genetic variants and environmental factors may exist. The gene-diet interactions for diabetes-related traits have been reported since mid-1990s [22]; nevertheless, the majority of these studies were performed in relatively small cohorts, case-control studies, and less clinical trials. With reliable interactions are discovered, the interaction information would be used to improve predictive accuracy, and the precision medicine informed by biomarker data would improve treatment outcomes. In addition, it will also be meaningful for the implications to public health, medical practice and biology.

Gene-Diet Interaction in Observational Studies

Most of the previous gene-diet interactions studies were performed in observational investigations such as case-control and cohort studies, and a small portion of those were conducted in clinical trial settings. Early studies were often concentrated on the selected genetic variants in candidate genes, while recent studies focused more on the GWAS-identified variants.

TCF7L2 is the strongest susceptibility gene associated with T2D by far. Quite a few studies testing interactions between *TCF7L2* variants and dietary factors, such as whole grains, fat, protein, carbohydrate, and Mediterranean diet (MedDiet) were emerging [23-26]. In the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam cohort, the *TCF7L2* rs7903146 genotypes were found to modify the inverse association between whole-grain intake and diabetes risk (P for interaction = 0.016). In the carriers of C allele, whole-grain intake was significantly in relation to a decreased diabetes risk (hazard ratio [HR] for 50 g portion/day = 0.86; 95% confidence interval [CI]: 0.75, 0.99); whereas the T-allele attenuated the associations to null (HR=1.08; 95 % CI: 0.96, 1.23) [24]. The investigators found that the *TCF7L2* rs7903146 variant also modulated associations between fiber intakes and T2D in a case-control study derived from the Malmö Diet and Cancer Study (MDCS) [26], which included 5,216 non-diabetic controls and 1,649 diabetes cases. The association between genetic effects with T2D risk increased with higher intake of dietary

fiber, with ORs ranging from 1.24 to 1.56 from the lowest to highest quintile of fiber intake (P for interaction = 0.049). The MedDiet is deemed to be an healthy dietary pattern, which includes proportionally high consumption of olive oil, legumes, unrefined cereals, fruits, and vegetables, moderate to high consumption of fish, moderate consumption of dairy products (mostly as cheese and yogurt), moderate wine consumption, and low consumption of meat and meat products. In a prospective study including 7,018 individuals with a median follow-up of 4.8 years, it was found that adherence to the MedDiet could reduce the increase in fasting plasma glucose and serum lipids levels related to *TCF7L2* rs7903146 [26].

Another widely validated and well accepted T2D-related genetic locus is zinc transporter-8 gene (*SLC30A8*). The gene encodes ZnT-8, which transports zinc from the cytoplasm into insulin secretary vesicles in pancreatic beta cells playing an important role in insulin synthesis and secretion. Zinc is an essential trace element found in most foods and facilitates catalytic, structural, and transcriptional actions [27]. Plasma zinc concentrations have been reported to be associated with impaired glucose regulation (IGR) and T2D risk in epidemiology studies. Recently, one study was conducted by the Cohorts for Heart and Aging Research in Genetic Epidemiology (CHARGE) consortium [28], including14-cohort meta-analysis to assesses the interaction of 20 genetic variants related to glycemic traits and zinc metabolism with dietary zinc intake (food sources), and 5-cohort meta-analysis to assess the interaction with total zinc intake (food sources and supplements) on fasting glucose levels among individuals of European ancestry without diabetes. The data suggested that higher total zinc intake might attenuate the glucose-raising effect of the A-allele of *SLC30A8* rs11558471. Besides the tentative evidence of interactions for variants in *SLC30A8* and total zinc intake on fasting plasma glucose concentrations, it was also found that higher whole-grain intake was associated with less reduction in fasting insulin in those with the insulin-raising allele of rs780094 (*GCKR*) (P for interaction = 0.006) [29]. However, no interaction between the selected genetic variants and dietary magnesium or dietary patterns was found.

In a study from China, the researchers reported a significant the interaction of *SLC30A8* rs13266634 with plasma zinc levels associated with T2D (P for interaction = 0.01) [30]. Each 10-μg/dl higher plasma zinc level was associated with a decreased risk of T2D with multivariate-adjusted OR of 0.87 (95% CI 0.85-0.90). The associations was more prominent in the TT homozygotes, each 10-μg/dl increment of plasma zinc was associated with 22% (OR, 0.78; 95% CI, 0.72-0.85) lower odds of T2D; while 17% (0.83; 0.80-0.87) and 7% (0.93; 0.90-0.97) lower odds were observed in the CT and CC genotypes, respectively. Summarily, the C allele of rs13266634 was associated with higher odds of T2D and higher plasma zinc was related to lower odds. *SLC30A8* rs13266634 modulated the inverse association of plasma zinc concentrations with T2D.

In addition, in another large prospective cohorts study from southern Sweden, significant interactions between the *IRS1* and *GIPR* variants with dietary fat and carbohydrate intakes on risk of incident T2D were recently reported [32,33]. A protective association between the *IRS1* rs2943641 T allele and T2D was restricted to women with low carbohydrate intake (P for interaction = 0.01) and to men with low fat intake (P for interaction = 0.02) [31]. Prospective cohort results showed that AA-genotype carriers of *GIPR* rs10423928 consuming high-fat low carbohydrate diets had reduced T2D risk, whereas high-carbohydrate low-fat diets benefitted the two thirds of population homozygous for the T-allele [32].

Of note, several potential conceptual or methodological limitations need to be acknowledged, since the majority of available gene-diet interaction studies have focused on single nutrient or food. Firstly, in a real world, the "single nutrient/food" approach may not adequately account for complicated nutrient interactions in free-living populations. The cumulative effects of combined nutrients/foods intake, such as dietary patterns or quality indexes, may be more appropriate to be used in estimating gene-diet interactions. Secondly, to use combined genetic effect in the gene-diet interaction tests is a reasonable and effective way, especially when the individual genetic variation effect is minor. A genetic risk score summing risk alleles for the established susceptibility loci from GWAS has been widely used to represent the overall genetic predisposition [33]. Even though less informatively at the biological level, the genetic risk score is a powerful method for demonstrating an interaction. In a previous and important study by Qi et al. [8], the authors calculated a genetic risk score using a simple count method under an additive genetic model, assuming that each single nucleotide polymorphisms (SNP) is independently associated with T2D risk. It was found that the Western dietary pattern was significantly associated with an increment risk of T2D only among those with a high genetic risk score (≥ 12) than in those with a low genetic risk score. Secondary analysis suggested the interaction was largely attributable to the red and processed meat component of the Western diet. They concluded that genetic predisposition might synergistically interact with a Western dietary pattern in determining diabetes risk in men.

In a cross-sectional study by Yokoyama K et al [35], investigators found that 1, 25-dihyroxyvitamin D (1, 25OHD) levels may be associated with better chronic kidney disease (CKD) stages in patients with T2D and this association was modified by vitamin D receptor (VDR) polymorphisms. The positive association between 1, 25OHD and CKD stage was steeper in FokICT and CC polymorphisms than FokITT polymorphisms.

Gene-Diet Interaction in Clinical Trials

Randomized intervention trials may act as an alternative approach for testing gene-diet interaction in prospective manner [36]. Randomization minimizes the potential confounding effects or reverse causation that often occurs in observational studies, which may gravely bias gene-diet interactions. Specifically, in a randomized diet intervention trial, interventions are prescribed and dietary factors are usually precisely defined. In addition, the results may provide more direct evidence to instruct genetic-targeted diet modifications in future public health and clinical practice, which is a unique strength to gene-diet interaction in randomized intervention trials [23]. However, a major challenge of most of the existing clinical trials is their power for detection of moderate gene-diet interactions due to relative small size.

The Diabetes Prevention Program (DPP) is so far the largest randomized controlled trial of lifestyle intervention and metformin for diabetes prevention. gene-lifestyle interactions on incident T2D risk have been widely tested in this trial, and significant interactions between lifestyle intervention and genetic variants at *TCF7L2* [36], *WFS1* [37], other established T2D-related loci [38, 39], established glucose- and insulin-associated loci [39], common and rare variants at the *MC4R* [40] and *SLC80A8* loci [41], as well as other candidate loci [42-44] have been reported. For example, a stronger association between the TT homozygote of *TCF7L2* rs12255372 and the diabetes risk was found in the placebo group (HR=1.81; 95%CI 1.19-2.75) than in the lifestyle intervention groups, which was characterized as increased intake of fiber, moderate exercise for at least 30 minutes per day and reduced intakes of total fat and saturated fat. Although test of interaction was not statistically significant (P for interaction > 0.10), these data suggested that healthy diet intervention may attenuate the genetic effects on T2D risk.

Tübingen Lifestyle Intervention Program (TULIP) is another randomized control clinical trial consisting of exercise and diet intervention with decreased intake of fat and increased intake of fibers (participants were instructed to eat at least 15 g fiber per 1,000 kcal), which found that the CC genotype of *TCF7L2* rs7903146 is significantly related to greater weight loss in participants with high fiber intake, but not in those with low fiber intake [45].

The Preventing Overweight Using Novel Dietary Strategies (Pounds Lost) is a randomized clinical trial to assess the possible advantage for reduced-calorie weight-loss diets that emphasizes different macronutrient contents varying in carbohydrates, fat and protein in 811 participants for 2 years [46]. In the Pounds Lost trial [47], the T2D-related *TCF7L2* rs12255372 significantly modified the effect of fat intake on changes in Body Mass Index, total fat mass, and trunk fat mass (all P < 0.05) at 6 months. Individuals with the *TCF7L2* rs12255372 risk genotype may reduce body adiposity by consuming a lower-fat diet. The *FTO* SNP rs1558902 was also reported to modulate dietary protein on 2-year changes in fat-free mass, total percentage of fat mass, and total-, visceral-, and superficial adipose tissue mass [48]. A high-protein diet may be beneficial for weight loss and improvement of body composition and fat distribution in individuals with the risk allele of the *FTO* variant rs1558902.

Several other T2D-associated genetic variants have also been found to modify diet interventions on weight change and improvement of insulin resistance in the Pounds Lost trial [49,50], such as *IRS1* SNP rs294364 and the amino acid metabolites related genotype *PPM1K* rs1440581. At 6 months, participants with the *IRS1* SNP rs294364 risk-conferring CC genotype had greater decrease in weight loss than those without this genotype in the highest-carbohydrate diet group; whereas the genetic effect was not significant in subjects assigned to the lowest-carbohydrate diet group (P for interaction = 0.03). Branched amino acids (BCAAs) or aromatic amino acids (AAAs) were recently reported to be associated with obesity, insulin resistance and T2D risk [51-53] and weight loss induced by dietary intervention [54,55]. The firstly identified SNP from amino acid metabolites GWAS was *PPM1K* rs1440581, which was found to modify effect of dietary fat on weight loss and changes in insulin resistance [50]. In the energy restricted high-fat diet group, at 6 months of intervention, the C allele of rs1440581was associated with less weight loss (adjusted means: TT, -6.7kg; CT, -5.8kg; CC, -4.1 kg, respectively, *P* for interaction = 0.001 in an additive model), whereas no significant genetic effect was observed in the low-fat diet group. The carriers of C allele had smaller decreases in serum insulin and insulin resistance than those without this allele in high-fat diet group, whereas an opposite effect was observed in participants assigned to the low-fat diet group (*P* = 0.02 and 0.04, respectively).

The fruitful data derived from gene-diet interaction analyses in the randomized clinical trials may provide a promising prospective of personalized direct response to dietary interventions. However, as mentioned above, replication, functional exploration, and translation of the findings into personalized diet interventions remain the chief challenges.

CONCLUSION

Though previous studies on gene-diet interaction have provided preliminary but promising evidence, it is notable that most of them are generally limited by lack of replication. Because of the observational nature of these studies, confounding and reverse causation are inevitable. Improvement in measuring dietary factors in population studies is another major issue. Study shows that moderate decreases in the accuracy of measurement of dietary factors may lead to a 20-fold reduction in statistical power to detect

an interaction [56]. Moreover, conventional statistical approaches are usually underpowered to detect meaningful gene-diet interactions. Hence, a range of new methods have been addressed these challenges, especially on a genome-wide scale [57,58]. Breakthrough in the field will heavily rely on advances in methodology development and collective efforts of well-designed, prospective cohorts with comprehensive dietary information. Large-scale collaborations to detect gene-diet interactions in the randomized controlled trials are urgently needed.

It remains debatable how to translate statistically significant interactions into biological interactions. Advance in high-throughput genotyping technology will facilitate the service of direct-to-consumer genetic testing; and raise great hope that genetic testing will pave the way to personalized prevention and medicine. It could be imagined that the information from genetic and molecular biomarker screening in patients will be taken into account in the prescription of lifestyle such as dietary choice and drug therapy for diabetes prevention or management. Public health practice will not be able to ignore the evidence from studies of gene-diet interactions in the near future.

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