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Interactions between Genetic Factors that Predict Diabetes and Dietary Factors That Ultimately Impact on Risk of Diabetes

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Abstract

Purpose of review—The purpose of this review is to summarize recent advances in investigations of interactions between established genetic and dietary risk factors for type 2 diabetes (T2D).

Recent findings—Several studies reported that dietary factors related with carbohydrate quality and quantity, such as whole grains and glycemic load, might interact with *TCF7L2* variants in relation to T2D risk. The genetic predisposition defined by the combination of ten established T2D risk alleles was found to modulate the association between Western dietary pattern (high intakes of red meat, processed meat, and low fiber) and T2D; a stronger association was observed in those with high-risk genetic profile. Variants in genes *HHEX*, *CDKN2A/2B*, *JAZF1*, and *IGF2BP2* were found to interact with prenatal nutrition in relation to T2D risk and glucose levels in later life.

Summary—The available data provide preliminary support for the gene-diet interactions in determining T2D. However, most findings have yet to be validated. Future studies will need agreed standards of study design and statistical power, dietary measurement, analytical methods, and replication strategies.

Keywords

gene; diet; interaction; diabetes

INTRODUCTION

Type 2 diabetes (T2D) has become a leading health problem throughout the world. It was projected that the number of individuals with T2D among adults will double from the current 171 million in 2000 to 366 million in 2030 [1]. The escalating epidemic of T2D is related to the substantial environmental changes over the past several decades: from a 'traditional' style to a 'Westernized' or 'obesogenic' style featured by increased access to highly palatable, calorie-dense foodstuffs and sedentary lifestyle. However, the validation of the true causality of lifestyle factors is not straightforward.

In addition, classical genetic research, including twin, adoption, and family studies, consistently supports genetic contributions to T2D [2,3]. However, until very recently, the

genes involved have been poorly understood. Using new genotyping technology, genome-wide association (GWA) studies have recently led to the discovery of a group of novel genes that were moderately but robustly associated with diabetes risk [4–8].

It has long been noted that not all people are affected equally by unhealthy lifestyles: some are more sensitive to the deleterious effects than others [9]. Such heterogeneity may reflect complex interactions between genes and environmental factors. The observations of the marked geographic variations in incidence of diabetes and the altered patterns of disease in migrant populations add additional evidence for this notion [10–12]. However, studies directly testing gene-environment interactions are sparse.

The purpose of the present review is to summarize the recent literature about the interactions between the established T2D susceptibility genes and environment, with focus on dietary factors (**Table 1**). The review will also briefly address the potential challenges lie in the studies and future directions.

1. The dietary and genetic risk factors for type 2 diabetes

Lifestyle factors especially obesity/overweight and physical inactivity have been consistently associated with increased risk of T2D [13–15]. In addition, accumulating data have demonstrated that dietary factors may also contribute to the risk. One line of evidence is from the associations between dietary patterns and T2D. The Mediterranean diet, which is rich in nuts, olive oil, fruits and vegetables, fish, moderate in alcohol and low in red meat, processed meat, refined carbohydrates and whole-fat dairy products, may protect T2D [16]. By contrast, a Western dietary pattern, characterized by high intakes of red and processed meats as well as refined foods, have been related to increased T2D risk [17,18].

Some dietary components may particularly affect T2D. In a meta-analysis of six cohort studies, a two-serving/day increment in whole grain consumption was associated with a 21% decrease in T2D risk [19]. Prospective and intervention studies consistently support the protective effects of moderate intake of alcohol especially red wine on T2D [20,21]. In addition, it was reported high intakes of total fat, trans fatty acids, saturated fats, and heme iron contributed to an increased risk, while omega-3 fatty acids, low glycaemic index (GI) foods, and coffee consumption might reduce the risk [22,23]. However, Most of the implicated dietary effects are viewed controversial and the causality is difficult to be elucidated.

The genetic effects on T2D have been consistently evidenced by family and twin studies [24, 25]. The first established diabetes variant Pro12Ala in *PPARG* gene was associated with about 15% reduction in diabetes risk, which is translated into a population attributable risk (PAR) of 25% [26]. A Glu23Lys polymorphism (E23K) in *KCNJ11* gene was associated with T2D in many studies. The PAR was 10.1% for the EK and KK genotypes combined [27]. *TCF7L2*, the gene with the largest effects on the risk of T2D identified so far [28], was associated with up to 2-folds increase in T2D risk and a PAR of 16.9% [29]. All these genetic effects have been replicated in GWA scans [5,8].

The efforts to discover the T2D genes were recently fuelled by GWA studies. Since the first report published in 2007, thus far nearly 20 new loci have been found in more than ten GWA studies, mostly in Caucasians [5,8,30]. Most newly identified gene variants contribute only modestly (10–20%) to the disease risk, and in together provided a slightly better prediction of T2D risk than the traditional environmental risk factors alone [31,32]. Two GWA studies in Asians identified *KCNQ1* as a new locus increasing individual odds of T2D by 30–40% [33, 34].

2. *TCF7L2*, diet, and diabetes risk

To date, *TCF7L2* is the strongest and most widely replicated locus associated with T2D [28, 29]. The interactions between *TCF7L2* variations and dietary factors have attracted some attention. In the US Diabetes Prevention Program (DPP) [35]. A stronger association between the TT genotype of *TCF7L2* rs12255372 and the diabetes risk was found in the placebo group (hazard ratio=1.81; 95%CI 1.19–2.75) than in the lifestyle-intervention groups (reduced intakes of total fat and saturated fat and increased intake of fiber; moderate exercise for at least 30 minutes per day; hazard ratio=1.24; 0.73–2.12). Similar results were observed for rs7903146 ($r^2=0.75$ with rs12255372; CEU in Hapmap). The data suggest that dietary intervention may modify the genetic effects.

TCF7L2 has been implicated in glucose homeostasis and insulin secretion [36,37]. Dietary factors such as carbohydrate quality and quantity may also affect these pathways. Recently, Fisher et al. [38] tested whether the risk-conferring T-allele of *TCF7L2* SNP rs7903146 might modify the protective effect of whole grains on diabetes risk in 2,318 randomized individuals and 724 incident T2D cases from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam cohort. Dietary intake of whole grains was assessed by a validated food frequency questionnaire (FFQ). It was found that 50 g portion/day whole-grain intake was associated with 14% (1–25%) reduction in diabetes risk among rs7903146 CC homozygote carriers; but was associated with slightly increased though not significant risk among the T-allele carriers (P for interaction= 0.016). The data suggest that the risk allele might lessen the beneficial effect of whole grains on T2D risk.

Cornelis et al. tested a similar hypothesis in the Nurses' Health Study (NHS) [39]. The analysis includes 1,140 diabetes cases and 1,915 controls. *TCF7L2* SNP rs12255372 was genotyped. Dietary intake was assessed with a semiquantitative FFQ. Several dietary components highly related to glucose metabolism, including dietary GI and glycemic load (GL), cereal fiber, and total carbohydrate were examined. Stronger associations were found between rs12255372 and T2D among individuals in the highest tertile of GL and GI, as compared with among individuals in the lowest tertiles of GL and GI. The P values for interactions were 0.03 for GL and 0.05 for GI. However, no significant interactions were observed for cereal fiber or carbohydrate intakes.

Dietary fat may also interact with *TCF7L2* variants in determining the risk factors for T2D. In a study of 1,083 European Americans, in which the participants were tested for their response to high-fat meal [40], significant interactions were observed between rs7903146 and PUFA intake (<7.36 or $\geq 7.36\%$ of energy intake) in relation to fasting plasma VLDL and postprandial responses for TG, chylomicrons, and VLDL concentrations. Carriers of the T allele who consumed higher PUFA exhibited higher fasting and postprandial lipid levels than CC participants. The genetic effects were not observed in those with lower intake of PUFA.

3. Gene-diet interactions for other established diabetes loci

Qi et al. recently examined the interactions between the genetic predisposition and dietary patterns in a prospective cohort of US men [41]. T2D-associated loci *HHEX*, *CDKALI*, *IGF2BP2*, *SLC30A8*, *WFS1*, *CDKN2A/B*, *TCF7L2*, *PPARG*, and *KCNJ11* were selected from the GWA studies; and a genetic risk score (GRS) was calculated for genetic predisposition [31]. The participants were grouped into low, median, and high genetic risk categories (GRS<10, 11–12, and >12; respectively). Based on the baseline dietary information, the factor analysis generated 2 major dietary patterns: a Prudent dietary pattern was loaded heavily with vegetables, legumes, and whole grains; and a Western dietary pattern [17]. The GRS interacted with Western dietary pattern in relation to diabetes risk (P for interaction= 0.02; Figure 1). The multivariable ORs of T2D across increasing quartiles of the Western dietary pattern were 1.00,

1.23 (95% CI: 0.88,1.73), 1.49 (1.06, 2.09), and 2.06 (1.48, 2.88) among men with a high GRS only. Further analyses indicate that intakes of red meat, processed meat, and heme iron might be the major foods/nutrient driving the interactions. These findings suggest that the adoption of a Westernized diet may increase diabetes risk especially among the genetically high-risk population.

Florez et al. [42] examined the interactions between T2D-associated *WFS1* variants [43] and diet/lifestyle intervention as predictors of diabetes incidence in 3,548 DPP participants. No associations were observed with diabetes incidence in the overall cohort. However, it was noted that carriers of the protective alleles of *WFS1* SNPs were less likely to develop diabetes in the intervention group, although the test for the interactions was not significant.

Two recent GWA studies identified the common genetic variants near *MC4R* gene were associated with obesity risk and insulin resistance [44,45]. *MC4R* gene is expressed in several sites in the brain and has been implicated in mediating most of the effects of melanocortin on food intake and energy expenditure [46]. In NHS, it was found that SNP rs17782313 near *MC4R* was associated with high intakes of total energy and dietary fat and protein. However, these dietary factors did not modify the genetic effects on obesity and diabetes risk [47].

4. Interactions between T2D variants and prenatal nutrition

The thrifty phenotype hypothesis states that malnutrition during fetal development lead to poor fetal and infant growth, and predisposes to adverse health outcomes [48]. According to the hypothesis, fetal adaptation to a low-caloric intrauterine environment may produce permanent changes in chromatin structure and gene expression profiles affecting insulin secretion and insulin resistance. Small birth size as a marker for fetal malnutrition, especially when followed by accelerated growth in childhood, is a risk factor for T2D [49,50]. These associations may be modulated by T2D variants, which are involved in glucose metabolism and insulin secretion [51]. An earlier study reported significant interactions between early malnutrition during midgestation and the *PPARG* Pro12Ala polymorphism in relation to impaired glucose tolerance and T2D [52]. Two recent studies provide further evidence.

In one study, variants of nine T2D loci, *TCF7L2*, *HHEX*, *PPARG*, *KCNJ11*, *SLC30A8*, *IGF2BP2*, *CDKAL1*, *CDKN2A/2B* and *JAZF1*, were tested [53]. The study includes 928 men and 1,075 women. 15.6% of the participants had developed T2D. Risk variants at the *HHEX*, *CDKN2A/2B* and *JAZF1* loci significantly interacted with birthweight to predict future T2D ($p=0.04$, 0.03 and 0.02 , respectively). A lower birthweight amplified the risk conferred by the pooled variants in nine T2D genes, and a higher birthweight compensated the genetic effects.

In another study, Van Hoek et al. [54] assessed the interactions between T2D susceptibility genes and fetal exposure to famine. Seven SNPs at genes *CDKAL1*, *CDKN2AB*, *HHEX*, *IGF2BP2*, *KCNJ11*, *SLC30A8*, and *TCF7L2* were determined in 772 participants of the Dutch Famine Birth Cohort, which is composed of individuals born around the time of the Dutch famine during World War II. Prenatal exposure to famine was defined as a daily food ration of the mother <1,000 calories during any 13-week period of gestation. The *IGF2BP2* polymorphism showed an interaction with prenatal exposure to famine on glucose level ($P = 0.009$). However, none of the polymorphisms interacted with birth weight. Taken together, these data may provide a clue that an individual's genetic background may modulate the response to prenatal nutrition and subsequently affect T2D risk caused by hypercaloric environment in later life.

5. Future directions

The tangible breakthroughs in genetic research have brought about enthusiasm that future evaluation of gene-environment interactions might achieve the same success. For gene-diet studies, similar to GWA studies, it will be important to pre-specify agreed standards of study design and statistical power, dietary measurement, analytical methods, and replication strategies. The classical case-control studies collect lifestyle information retrospectively and are vulnerable to recall bias, and not suitable to test the interactions. Large-scale prospective cohorts allow for unbiased assessment of lifestyle in subjects prior to the diagnosis of disease, and therefore are the optimal design [55].

The ability to detect gene-diet interactions will largely depends on the accuracy of dietary measurements. Misclassification in dietary assessment may limit the study power. This is particularly damaging if the true strength of the interactive effects are modest. Weighed diet records can theoretically provide the most accurate assessment and multiple 24-h dietary recalls can provide excellent detail of intake. However, these methods are usually not realistic in large population studies due to heavy respondent burden, poor compliance, and the cost of data entry [56]. Food frequency questionnaires are the most cost-effective tool for assessing long-term intake, particularly for micronutrients with high day-to-day variability, although erroneous self-reporting of these components is a well-known problem.

Most published studies on gene-diet interactions limit to the established T2D loci. One way to get more insights into the complexity is to expand to hunt for more loci associated with T2D risk factors, and eventually to the whole genome. Recently, GWA studies have revealed many novel loci determining the risk factors for T2D, such as insulin and glucose concentrations, hypertension, and uric acids [57–59]. These genetic variants likely increase T2D in high-risk environment. In addition, the tremendous success of hypothesis-free GWA scanning suggests that such an approach can be also applied in gene-diet interaction analyses. Because the considerable diversity in dietary intakes across different populations and the varying measurement errors, replication will be a major challenge in future studies. In addition, the strengths of both the genetic and dietary effects may change across life, and therefore, the gene-diet interactions may be more likely to be identified at certain stages of life than others (Figure 2).

Estimates of the heritability for T2D range from 30% to 40% [2,60]. However, the newly identified genes in together explain only a small proportion of the individual risk of T2D. Large number of genetic variants accounting for the genetic component of diabetes risk has yet to be determined. Rarer variants and structure variants such as CNVs may be primarily responsible for the missing heritability [61]. However, the genotyping and analytical tools to detect these variations are premature and limit the test for interactions.

6. Conclusions

While it becomes widely accepted that genetic factors may interact with environment in affecting T2D risk, reliable evidence is sparse. During the past year, several studies have assessed the interactions between the newly identified diabetes genes and dietary intakes. These findings, while interesting, have for the most part not been validated. Therefore, we should be cautious in interpreting the gene-diet relations without further evidence. Since the quantification of dietary intakes is notoriously difficult, it will remain a formidable challenge to obtain stable replications for most of such observations. Further research will require very large sample size, a better assessment of dietary exposure, and well-designed analyses with valid samples for replications.

Individual risk-based, or ‘personalized’, dietary interventions have long been proposed as an attractive target in future treatment or prevention efforts tailored to the reduction of diabetes. This is one of the goals of the recently announced Genes, Environment, and Health Initiative of the National Institutes of Health. A thorough understanding of the gene diet (also other environment factors) interactions underlying diabetes may foster more efficient intervention strategies and thus may assist in improving the quality of life for affected individuals.

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Abbreviations

SNP	single nucleotide polymorphism
T2D	type 2 diabetes
GWA	genome-wide association
GI	glycemic index
GL	glycemic load
TG	triglycerides
VLDL	very-low-density lipoprotein
PUFA	polyunsaturated fatty acids
OR	odds ratio
CNV	copy number variation

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Figure 1.

Odds ratios of diabetes risk according to joint classifications of western dietary pattern score (in quartiles) and genetic risk score (GRS, <10, 10–11, and ≥12). The analyses were adjusted for age, BMI, smoking, alcohol consumption, physical activity, family history of diabetes, and total energy intakes. Data are taken from reference (41).

Figure 2.

Schematic representation of gene–diet interactions across life span. Prenatal nutrition interacts with genetic factors in determining diabetes risk in later life; The genetic effects are decreasing and dietary effects are increasing in strength from young to old age; the strength of gene–diet interactions may vary across life span.