Review Article

Gene-environment interactions and type 2 diabetes

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Type 2 diabetes (T2D) caused by the complex interplay of both genetic and environmental factors, is a serious public health issue. Compelling evidence from epidemiological studies has highlighted that an unhealthy lifestyle, such as obesity, physical inactivity and poor diet are significant drivers of the epidemic of T2D. Meanwhile, recent genome-wide association studies (GWAS) have identified a large number of T2D and glycemic traits loci. Emerging data emphasize the critical role that gene-environment interactions have played in the development of T2D. Identifying the genetic, environmental factors and their complex interplays may help elucidate the biological pathways of T2D, identify the high-risk groups and characterize heterogeneity in intervention programs. This review summarized the studies investigating gene-environment interactions of T2D.

Key Words: genome-wide association studies, gene-environment interaction, type 2 diabetes

INTRODUCTION

Type 2 diabetes (T2D) has increased rapidly throughout the world over the past several decades.[1] The total number of T2D will be up to 438 million by 2030.[1] T2D has contributed to considerable adverse effects on microvascular and macrovascular complications, which is a huge health and economic burden for both individuals and health systems.[2] T2D is a complex disease that is considered to be caused by a complex interplay between genetic and environmental factors. Recently, more and more studies have been focusing on interactions between diet or lifestyle and genetic factors on T2D. The gene-environment interactions (G×E) study is meaningful to unveil the mechanism of T2D, identify the high risk individuals, distinguish the heterogeneity in response to the intervention and optimize the interventions.[3] Elucidating these interactions could help improve precision prevention of T2D.[4] This review summarized recent advances in investigations of lifestyle, genetic risk factors as well as their interactions for T2D.

In this review, we focused on the modifiable environmental risk factors, such obesity, physical activity, sleep and habitual diet. Hence, ageing was not discussed in our review. Genetic factors were selected based on both the candidate approach and genome-wide association study (GWAS).

ENVIRONMENTAL RISK FACTORS OF T2D

Obesity

Overall obesity and central obesity were both risk factors for T2D. Elevated body mass index (BMI) as an indicator of general adiposity was well recognized as a risk factor for insulin resistance and diabetes.[5] Moreover, the relationship between BMI and risk of insulin resistance and T2D showed heterogeneity across different populations. Evidence has suggested that Asians have lower level of BMI in comparison with Europeans when they were recorded as T2D;[6] this risk difference may reflect a genetic susceptibility. It is worth noting that even among Asian population, variation exists in the predisposition to diabetes. A study conducted in Singapore involving three ethnics namely Chinese, Malays and Indians showed Indians were at highest genetic predisposition to T2D in comparison with other ethnics. The difference between Chinese and Malays could be explained by general adiposity. However, there were still unexplained factors contributed to the insulin resistance in Indians after adjustment for BMI and BMI-adjusted waist circumference.[7]

Physical activity

A dose-dependent inverse association was observed between physical activity and risk of T2D, which may be partially mediated through decreasing adiposity. All types of physical activities including ≤7 hours leisure-time,

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vigorous or low intensity physical activities were associated with a lower risk of T2D.[8] Further, sedentary behavior was an risk factor of T2D independent of physical activity.[9] Individuals can be active once they reach the recommended physical activity level and be sedentary as well.

Sleep duration and quality

The relationship between sleep duration and risk of T2D was U-shaped; both short and long sleep duration were associated with a higher risk of T2D through activation of pro-inflammatory and increasing arterial stiffness.[10-12] Sleep patterns and sleep qualities were also associated with risk of T2D.[13]

Smoking

Smoking is the leading avoidable risk factor for a wide range of diseases. The relationship between cigarette smoking and risk of T2D has been widely studies: smoking was associated with an increased risk of T2D for the current smokers in a dose-dependent manner.[14] An Pan et al. showed that both active and passive smoking were associated with a higher risk of T2D. The observed risk substantially reduced among the long-time quitters.[15] In addition, weigh gain with smoking cessation was associated with a higher risk of T2D,[16] which indicated during the smoking cessation, weight management was critical for reducing the risk of T2D.

Diet

Evidence of the relationship between individual nutrients, foods and risk of T2D has been extensively investigated. Low circulating concentrations of vitamin D was associated with an increased risk of T2D; and the relationship has been warranted to be causal in Mendelian Randomization studies.[17,18] Red and processed meat was positively associated with an increased risk of T2D;[19] whereas low-fat dairy products consumption and coffee consumption were associated with a lower risk of T2D.[20,21]

Dietary pattern approach, an emerging approach considering the interactions between nutrients and physical properties of goods has been widely used to examine the associations between diet and health outcomes.[22] Healthy dietary patterns, such as Mediterranean diet, alternative Healthy Eating Index-2010 (AHEI-2010) and Dietary Approaches to Stop Hypertension diet (DASH), which all highlight whole grains, fruits, vegetables, nuts and legumes were associated with a lower risk of T2D,[23] whereas Western dietary pattern, which emphases red meat, fat and sugar sweetener beverages was associated with a higher risk of T2D.[24]

Adherence to healthier lifestyle is beneficial for the T2D patients

Besides the relationship between environmental risk factors and risk of T2D among the general population, adherence to a healthy lifestyle could also benefit the T2D patients to decrease the subsequent morbidity and mortality. Evidence showed that smoking cessation without subsequent weight gain was associated with a lower risk of cardiovascular disease and all-cause mortality among the patients with T2D. Even among the T2D patients with a subsequent weight gain after quitting smoking, the inverse association was persistent between cessation and mortality.[25] Moreover, higher consumption of nuts and polyunsaturated fatty acids (PUFAs) were also associated with a reduced risk of development of cardiovascular disease among the patients with T2D.[26,27]

GENETICS OF T2D

Although the environmental risk factors in relation to risk of T2D have been extensively examined, it has been well noted that the responses to the environmental factors varies substantially between individuals; and such difference in susceptibility to T2D risk was considered to have a heritable component. Genetic studies have demonstrated that T2D risk is substantially influenced by genetic factors. It has been estimated that approximately 35% of T2D could be explained by heritability.[28] Approaches used to identify disease-causing genes have evolved rapidly. The traditional methods for mapping disease-causing genes include linkage analysis and candidate gene approach.[29] Over the past several decades, many genes including NOTCH2, ZBED3, PPARG, IRS1, WFS1, HNF1A, HNF1B, HNF4A, TCF7L2, and ADIPOQ have been identified by the aforementioned methods.[30-33]

In the past decade, waves of GWAS featuring larger samples, denser genotyping arrays supplemented and richer ethnic diversity have brought the total number of independent T2D associations to more than 400 loci including European, Asian, Hispanics/Latinos and African-American ancestry.[34-37] The first GWAS by meta-analyses of Glucose and Insulin-Related Traits Consortium (MAGIC) identified MTNR1B influenced fasting glucose levels[38] and the GWAS meta-analysis of T2D by the DIAGRAM consortium identified six novel loci.[39] In other ethnic groups, a variant near PAX4 as a novel locus for T2D in Chinese was identified in a meta-analysis of GWAS.[40] PAX4 mutations were first found in Asian population[41] but seldom identified in those of European descent.[42] In the Middle East and African populations, T2D susceptibility loci identified through GWAS showed differential associations with T2D in two Arab populations,[43] requiring larger sample size study and GWAS meta-analysis to clarify the true genetic association with T2D and glycemic traits in other ethnic groups. Mahajan et al. conducted a multi-ethnic meta-analysis of GWAS, and they observed significant excess in the directional consistency of T2D risk alleles across ancestry groups and identified seven new T2D susceptibility loci,[44] Although the genetic prediction did not perform better prediction beyond the traditional environmental risk factors, genetic disposition could be helpful to stratify the population to provide precision prevention strategies on high-risk groups.[45,46] In addition, a new method of generating polygenic predictor including 2.1 million of common DNA variants to quantify the obesity susceptibility provided new opportunities for deriving polygenic predictor of T2D to improve the performance of prediction.[47]

RECENT STUDIES × LIFESTYLE INTERACTIONS

Though GWASs have identified more than 400 loci robustly associated with T2D and glycemic traits, the iden-

tified genetic variants so far explained a minority of T2D heritability.[48] The G×E study is useful for gaining a better understanding of the biological pathway, explaining the missing heritability and identifying the susceptible population.[49,50] Selected gene × environment interaction are presented in Figure 1.

Candidate gene × lifestyle

The candidate-gene approach has identified several loci that play substantial roles in the T2D etiology. Variants within these loci have been studied for G×E study with related lifestyle risk factors on T2D and glycemic traits. For instance, PPARG gene is an extensively studied candidate gene for T2D.[51-57] A cross-sectional, population-based study suggests an interaction between Pro12Ala polymorphism of PPARG2 and dietary monounsaturated fatty acids (MUFA); obese people with Ala-12 allele have higher insulin resistance when their MUFA intake is low.[51] Nelsona et al studied 216 Hispanic pedigrees (1850 nuclear families) and 236 non-Hispanic white (NHW) pedigrees (1240 families) and found that the Pro12 allele was associated with T2D only among those with low physical activity, or high polyunsaturated fat intake in NHWs.[54] A study of general population indicates strong genetic and nutritional interaction on T2D risk at the PPARG variants found that high fat consumption was associated with an increased T2D risk among GG and CC homozygotes, but not in A and T carriers.[55]

IRS1 gene plays an important role in insulin function. In 1993, it was reported that Gly972Arg polymorphism in IRS1 was associated with T2D.[58] Recent years, several studies have investigated the interaction effects between SNPs in IRS1 gene and environmental factors on T2D risk. Cross-sectional population-based surveys indicated significant and consistent interactions between circulating 25(OH)D and IRS1 variants on insulin resistance in the Boston Puerto Rican Health Study, African-American, non-Hispanic white, and Hispanic. Participants with different genotypes of IRS1 rs2943641 exhibited differential benefited from high circulating 25(OH)D with the reduced risk associated with insulin resistance and T2D risk.[59] Furthermore, the Malmö Diet and Cancer cohort demonstrated that IRS1 rs2943641 interacted with carbohydrate and fat intakes on T2D incident. A protective association was restricted to women with low carbohydrate diet intake and men with low fat diet intake.[60] Of note, the inconsistencies and the significant findings need to be replicated.

GWAS genes × obesity

Among the GWAS identified diabetes loci,[34,61-65] TCF7L2 gene, which is discovered by linkage studies initially, is a consistently replicated gene for T2D.[66-70] Previous meta-analysis demonstrated that the genetic effect of TCF7L2 rs7903146 on diabetes risk can be modified by BMI: the lower the BMI was, the higher the gene effect was.[68] A case-cohort study of 2318 individuals and 724 incident T2D cases from the European Prospective Investigation into Cancer and Nutrition (EPIC)-Potsdam cohort showed the TCF7L2 rs7903146 T-allele modified the inverse association between whole-grain intake and T2D risk. Whole-grain intake was inversely associated with T2D risk among rs7903146 CC homozygote carriers; the T-allele negated the protective effect of whole-grain intake.[69] EPIC-Inter Act study also illustrated an interaction between TCF7L2 variants and coffee intake on risk of T2D.[71] In addition, TCF7L2, NOTCH2 and ZBED3 showed significant interactions with dietary fiber intake on incident T2D in a large cohort over 15 years follow up.[72]

GWAS genes × diet

Several variants were also shown to interact with diet or lifestyle factors in relation to T2D risk. For example, low

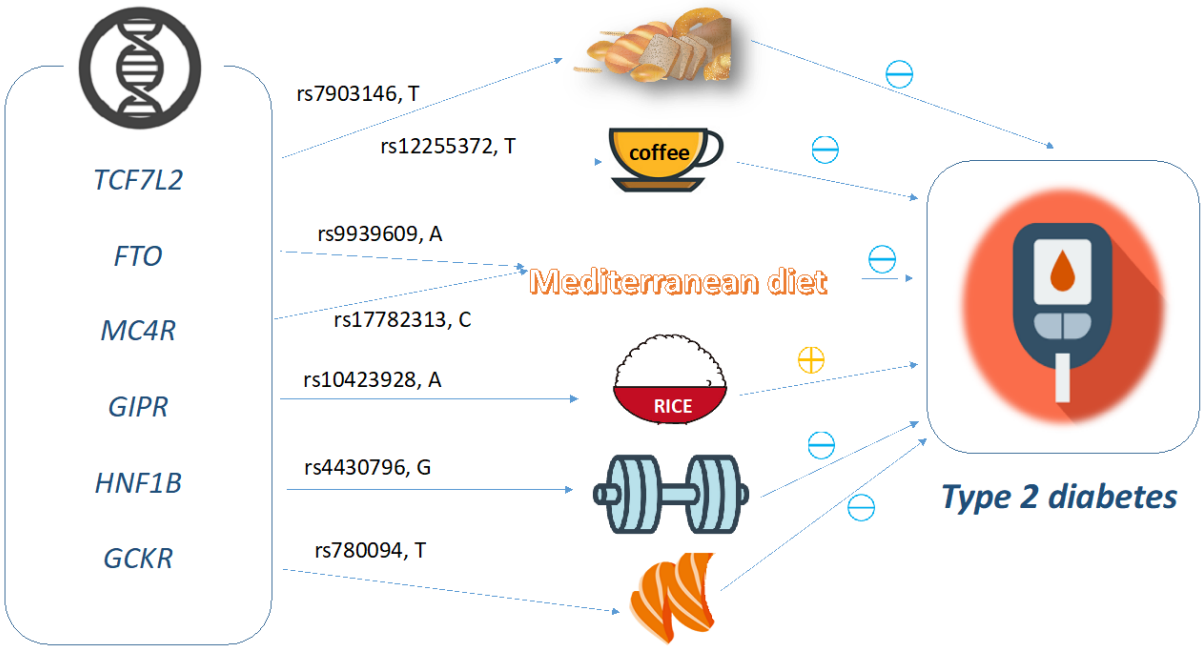

Figure 1. Selected gene-environment interactions on type 2 diabetes. Environmental factors including whole grain intake, coffee consumption, Mediterranean dietary pattern, rice consumption, physical activity, fish consumption may modify the association between genetic susceptibility to T2D.

birth weight might influence the genetic association of common variants (HHEX, CDKN2A/2B and JAZF1) with T2D.[73] A case-control study among 7,052 participants with high cardiovascular risk showed consistent gene-diet interactions with adherence to the Mediterranean diet both for the FTO-rs9939609 and the MC4R-rs17782313, suggesting that the association of the FTO-rs9939609 and the MC4R-rs17782313 polymorphisms with T2D depends on overall diet habits and that adherence to the Mediterranean diet may counteract the genetic predisposition.[74] In addition, the EPIC-Norfolk study found no evidence of interaction between Mediterranean diet and GCKR for lipids or HbA1c.[75] However, this is a cross-sectional study, which does not allow temporal relationships to be examined. A large two years dietary intervention study demonstrated that carriers of the risk alleles of FTO variant rs1558902 may benefit more in reducing insulin resistance if they choose high-fat weight-loss diets rather than low-fat diets, but the association between FTO variants rs9939609 and insulin sensitivity was not modified by macronutrient intakes.[76] It suggested a protective association between vegetables and fish consumption and hypertriglyceridemia dependent on the genetic background. In particular, high fish intake diet may benefit TT-genotype carriers of the GCKR variants more and CC-genotype carriers may derive more benefits from a high consumption of vegetables.[77] Meta-analyses illustrated that MTNR1B variant rs1387153 with each additional 1% carbohydrate intake carrying T allele, was associated with a 0.003 mmol/L higher fasting glucose.[78] The genetic effect of PEPD variant rs3786897 on T2D risk may be modulated by MUFA intake, which suggested that high MUFA intake had a favorable effect among GA-genotype and AA-genotype carries.[79]

GWAS genes × physical activity

Besides the habitual diet factors, the associations between gene and risk of T2D were also modified by physical activity. The associations between FTO and obesity and T2D were modified by habitual physical activity. A meta-analysis showed that the risk estimates of FTO on obesity reduced 30% among the individuals who were physical active in comparison with those sedentary individuals,[80] which indicated physical activity could compromise the genetic susceptibility.

T2D sub-phenotypes gene and environment interaction on T2D

T2D is a heterogeneous disease involving different pathways: impaired beta cell function and insulin resistance. To be more specific, cluster method has suggests five pathways driving T2D, namely beta cell cluster, proinsulin cluster, obesity cluster, lipodystrophy cluster and liver/lipid cluster.[81] Evidence has suggested that using T2D sub-phenotype could be the direction to identify the high risk population to provide strategies for precise prevention.[82] Recently, evidence has shown that genetic markers associated with glycemic traits and beta-cell function in children are associated with T2D of children.[83]

FUTURE DIRECTION

In future, genome-wide interaction analyses will significantly advance our understanding of the development of T2D. GWAS analysis of main effects might miss important genetic variants specific to subgroups of the population. Therefore, novel innovative analytical methods to maximize statistical power in genome-wide interaction analyses need to be developed. In addition, with the rapid development of comprehensive "omics" approaches, how and to what extent genes regulate products at genomics, epigenetics, transcriptomics, proteomics, and metabolomics levels in response to exposed non-genetic factors becomes the subject of intense investigation. Information from studies of metabolomics and gut microbiome unveiled by omics technologies will provide new insights on the gene-environment interaction role in T2D and glycemic traits. The gene-environment interaction using "omics" approaches in large cohorts need to be conducted in the future.

CHALLENGES AND SUMMARY

Despite progress in understanding gene-environment interaction underlying the development of T2D, we are still facing several challenges. First, measurement errors in the assessment of environmental factors such as diets and lifestyle are inevitable. It has been demonstrated that moderate decreases in the accuracy of measurement of environmental factors may lead to a 20-fold reduction in statistical power to detect an interaction.[84] Second, a major factor limiting progress in this field is the limited statistical power to detect gene-environment interactions in T2D accurately.[85] A large sample size of population-wide biobanks will considerably contribute to the identification of gene-environment interactions on complex diseases. Third, previous inconsistent results need replication or more detailed follow-up. It is encouraged to conduct replication studies and to publish both positive and negative findings in other cohorts in a variety of populations to indicate that this association is not limited to specific population.[85]

In summary, substantial progress in identifying genetic, environmental markers and their interplays underlying the development of T2D have been made. Understanding the genetic basis of diabetes and the extent to which genotypes modify the response to risk factors and preventive interventions might help tackle the rising prevalence of diabetes, improve treatment, and optimize the quality of life.

AUTHOR DISCLOSURES

The authors declare no conflict of interest.

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