



Gene-lifestyle interplay in type 2 diabetes

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Type 2 diabetes (T2D) is widespread, affecting the health of hundreds of millions worldwide. The disease results from the complex interplay of lifestyle factors acting on a backdrop of inherited DNA risk variants. Detecting and understanding biomarkers, whether genotypes or other downstream biological features that dictate a person's phenotypic response to different lifestyle exposures, may have tremendous utility in the prevention of T2D. Here, we explore (i) evidence of how human genetic adaptation to diverse local environments might interact with lifestyle factors in T2D, (ii) the key challenges facing the research area of gene \times lifestyle interactions in T2D, and (iii) the solutions that might be pursued in future studies. Overall, many preliminary examples of such interactions exist, but none is sufficient to have a major impact on clinical decision making. Future studies, integrating genetics and other biological markers into regulatory networks, are likely to be necessary to facilitate the integration of genomics into lifestyle medicine in T2D.

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Current Opinion in Genetics & Development 2018, 50:35–40

This review comes from a themed issue on **Molecular and genetic basis of disease**

Edited by **Ines Barroso** and **Jose Florez**

<https://doi.org/10.1016/j.gde.2018.02.001>

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Introduction

The burden of type 2 diabetes (T2D) is not equally arrayed, as susceptibility to diabetogenic environmental factors tends to segregate by ethnicity and within families [1*,2]. This observation has led many to recognize that diabetogenic environmental factors are likely to convey

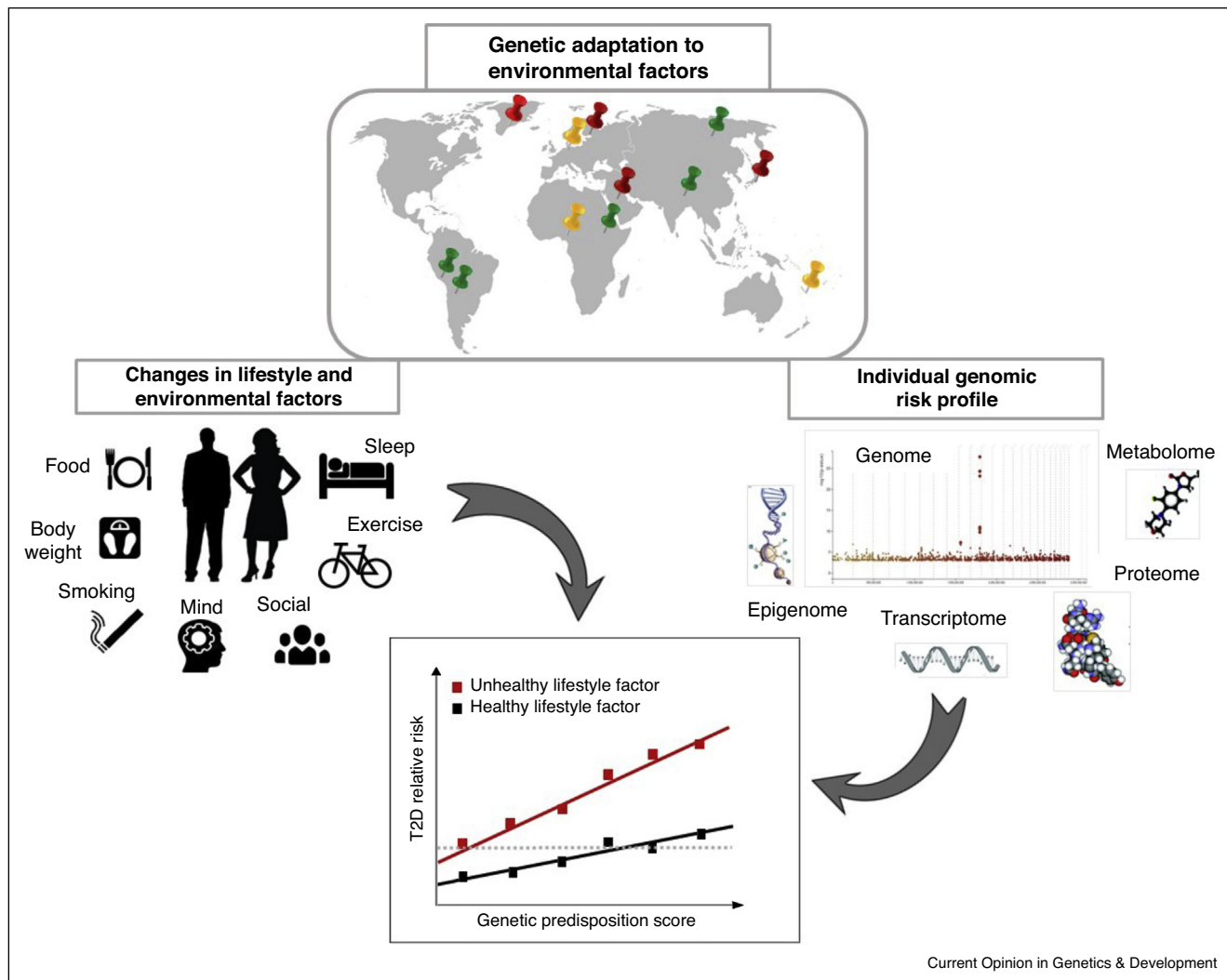
different effects depending on the genetic background of the individual; it may be necessary to understand this concept, often referred to as 'gene \times lifestyle interaction', if the etiology of T2D is to be adequately dissected, and lifestyle medicine is to serve its full potential.

The major scientific guidelines for the prevention and treatment of virtually all non-communicable diseases emphasize healthy lifestyle choices as the frontline intervention to prevent disease. However, as is the case with exposure susceptibility, the success of lifestyle medicine in the prevention and treatment of diabetes varies substantially from one person to the next [3**,4]. Much of this may be attributable to adherence to therapeutic recommendations [5]. Nevertheless, there also appears to be a meaningful heritable component to the effects of lifestyle in cardiometabolic disease [6]. Moreover, both gene \times gene and gene \times environment (G \times E) interactions are likely to be important determinants of allelic specific expression, such that between one third and one half of the observed variance in allele specific expression is owing to non-additive genetic effects, including interactions [7]. In combination, these findings raise the possibility that genetic data may be useful in the optimization of lifestyle medicine.

Evidence of genetic adaptation to environmental factors

The first empirical evidence that genes govern phenotypic adaptations to environmental cues came from studies of temperature and eye facet formation in *Drosophila* [8]. Garrod is often cited as the first to propose mechanistic interactions between genes and food in humans, although none of this early work focused on energy metabolism or diabetes [9]. Indeed, the first commentary about genetic selection in diabetes came decades later, when Neel proposed the "Thrifty genotype hypothesis", whereby he posited that the high rates of diabetes in contemporary American Indians are the consequence of evolutionary adaptations that favored efficient use and storage of energy during famine and migration [10**]. Although the Thrifty genotype hypothesis is often discussed in the context of genetic adaptations to extreme environmental conditions, there is little empirical evidence to support the existence of thrifty genes [11]. One intriguing exception though, is of an obesity-predisposing variant at *CREBRF* (p.Arg457Gln), which was discovered in contemporary Samoans [12**]; the variant, which may have protected against starvation during arduous ocean migrations, promotes fat storage and reduces cellular energy metabolism, modestly increasing risk of obesity, but paradoxically reducing the risk of T2D.

Figure 1



Gene \times lifestyle interplay in type 2 diabetes. Schematic representation of $G \times E$ interaction in T2D. The spread of humans across the globe has led to genetic adaptation to diverse local environment (red; adaptation to dietary components such as diet rich in fatty acids or cereals, green; genetic adaptation to geographic distribution such as altitude, yellow anthropometric adaptation such as body weight or height. Adapted from Fan S, Hansen ME, Lo Y, Tishkoff SA. **Going global by adapting local: A review of recent human adaptation.** *Science*. 2016, **34**:54–59). The enriched genome (Manhattan plot for T2D based on the UK Biobank data; available from <https://biobankengine.stanford.edu>) is unlikely to adapt to rapid changes in environmental factors, therefore genetic susceptible individuals are at higher odds to develop the disease. In addition, downstream genomic information, including epigenomics, transcriptomics, proteomics or metabolomics markers is likely to offer novel insights in the interplay between genomics and lifestyle factors.

The very rapid emergence of non-autoimmune diabetes in certain indigenous groups, such as Micro-Indonesian Islanders, American Indians, and Greenlandic Inuit, in concert with rapid changes in the environment, has reinforced the belief that T2D is caused by the joint effects of genetic predisposition and environmental triggers [12^{**},13,14^{**},15^{*}]. Figure 1 illustrates how genetic adaptation to diverse local environments and downstream genomic information might interact with lifestyle factors in T2D. The Pima Indians of Arizona, for example, have contributed massively to our understanding of diabetes through their decades-long engagement in NIH-led

research. The Pima, like many of the indigenous populations of North America were displaced of their land and customs by the Reclamation Act of 1902. The consequential shift away from subsistence farming, toward economically and nutritionally impoverished urban lifestyles, triggered epidemics of obesity and diabetes that persist to this day. The very high lifetime prevalence (>50%) and the very early onset (often in adolescence) of non-autoimmune diabetes in the Pima [13] is in stark contrast to the more favorable disease demographics of European-ancestry populations living in similar circumstances, implicating ethnic-specific catalysts, such as genes.

Moreover, the prevalence of diabetes in the closely-related Mexican Pima, who at the time of the study still subsistence farmed, was ~10% in the 1990s [16], suggesting that although the Pima's susceptibility to diabetes might have a genetic basis, lifestyle is a key modulator of risk. Nevertheless, despite extensive genetic research in this population, little definitive evidence of significant G × E interactions or Thrifty genes has emerged.

By contrast, recent studies of Greenlandic Inuit have yielded convincing examples of how environmental pressures have enriched the human genome with specific loci that affect a person's response to foods and nutrients [14[•],17]. For example, allelic heterogeneity at *FADS1* and *FADS2* affect fatty acid desaturase activity, which appears to have facilitated selection under varying environmental/dietary conditions [17]. *FADS* mutations that the Greenlandic Inuit carry are associated with increased levels of linoleic acid and α -linolenic acid (short-chain PUFAs), and decreased levels of arachidonic acid and eicosapentaenoic acid (long-chain PUFAs); accordingly, it appears that these specific *FADS* variants may be frequent in this population because fatty marine animals were a dominant dietary component throughout the Inuit's recent evolution [14[•]]. By contrast, in European populations, selection has favored alleles associated with a decrease in linoleic acid levels and an increase in eicosapentaenoic acid. [17]. A recent multi-cohort analysis, comprised of adults from Europe and North America, showed that Inuit-specific SNPs at the *FADS* locus do not appear to modify the relationship of omega 6 fatty acids biomarker levels and incident T2D [18].

Cold exposure may also have driven the selection of loci implemented in energy metabolism in the Greenlandic Inuit. For example, a highly-prevalent (minor allele frequency [MAF] of 17%) nonsense variant (p.Arg684ter) at the Tre-2/BUB2/cdc 1 domain family 4 (*TBC1D4*) locus severely inhibits post-prandial cellular glucose uptake in Greenlandic Inuit [15[•]]; the variant is present in other Inuit populations, but essentially absent in non-Inuit. The protein encoded by *TBC1D4* (and *TBC1D1*) (Rab-GTPase-activating proteins/AS160) regulates the effects of insulin and exercise on skeletal muscle oxidation and transportation of glucose and fatty acids (see [19]). In mice, variants at *Tbc1d1* modulate exercise-dependent uptake of glucose into skeletal muscle and body weight, although supportive data in humans has not been published. However, Greenlandic Inuit carrying both copies of p.Arg684ter variant are at relatively high risk of T2D (odds ratio = 10.3) [15[•]], owing to decreased post-prandial glucose transport caused by muscle-selective loss of the long *TBC1D4* isoform and corresponding reductions in GLUT4-mediated insulin-stimulated glucose uptake. Furthermore, a thymine for cytosine substitution (at nucleotide 1087 in exon 3, which causes a premature stop at codon 363) has been shown to convey an

exaggerated first-phase insulin response to glucose in people with acanthosis nigricans [20]. Whether phosphorylation of AS160 and GLUT4 translocation are affected by *TBC1D4* variants or whether such variants interact with exercise in outbred populations is unknown.

Elsewhere, a common risk haplotype in the *SLC16A11* locus (MAF ~40–50% among people of Mexican or Latin American descent, but rare among Europeans and absent in Africa) explains ~20% of the increased T2D prevalence in Mexico [21]. A recent study of American Indians found a strong interaction with body mass index (BMI) and rs75493593 in T2D risk, such that the association of the variant and diabetes was strongest in leaner individuals [22]. Although the mechanism of action is not known, lower levels of monocarboxylate transporter 11 (the protein encoded by *SLC16A11*) in the plasma membrane of primary human hepatocytes affects changes in fatty acid and lipid metabolism that may affect glycemic control in the face of weight gain or weight loss [23].

Evidence of the gene × lifestyle interplay in T2D and obesity

Many of the established T2D-associated loci have been examined for their potential roles in gene × lifestyle interactions, with the largest studies having been performed in European-ancestry populations. The European Prospective Investigation of Cancer-InterAct consortium (EPIC-InterAct), for example, undertook the largest study to date on this topic ($n = 12\,403$ incident cases and 16 154 healthy controls), studying the interactions of 58 established T2D-associated variants with Mediterranean diet and physical activity; these analyses yielded no convincing evidence of interactions at an individual gene variant or burden-score level [24]. The EPIC-InterAct cohort has since been used to examine gene interactions with dietary fiber [25], dietary factors influencing body iron status [26], and macronutrient intake [27[•]], although no compelling evidence has been forthcoming. The Cohorts for Heart and Aging Research in Genomic Epidemiology Consortium (CHARGE) has also examined interactions between many of the same loci and quantitative glycemic traits. Those analyses provided tentative evidence of interactions between dietary fiber and zinc intake with variants at *GCKR* [28] and *SLC30A8* [29] respectively. Several reports from single prospective cohorts have also yielded suggestive evidence of gene × lifestyle interactions in incident diabetes (reviewed in [30]), although independent replication analyses are conspicuously absent.

Evidence of gene × lifestyle interactions is considerably stronger for obesity. There are now many large-scale observational studies in which evidence of gene × lifestyle interactions for specific loci and for sets of loci have been explored. Variants with very strong association signals with BMI are especially strong candidates

for $G \times E$ interactions *per se* [31], with the single most compelling signal located at *FTO* [32]. A decade ago, evidence began to emerge of interactions between variants at the *FTO* locus and physical activity [33], which, within a year, were followed by single-cohort analyses of *FTO* \times lifestyle interaction [34–36]. Subsequently, comprehensive consortia-based analyses confirmed these initial findings, demonstrating that the estimated risk of obesity conferred by *FTO* may be attenuated by $\sim 30\%$ by a physically active lifestyle [32,37]. The evidence of interactions at the *FTO* locus have recently been extended to include multiple additional lifestyle exposures: a recent analysis in the UK Biobank cohort ($n \sim 120\,000$ adults), for example, reported statistically robust interactions between an *FTO* variant (rs1421085) and frequency of alcohol consumption, sleep duration, dietary salt, and diet *per se*, as well as physical activity [38]. Epidemiological analyses focused on genetic risk scores for obesity (usually constructed using BMI-associated risk alleles) have also yielded compelling evidence of gene \times lifestyle interactions for physical activity [39], fried food consumption [40], sugar-sweetened beverages [41^{••}], and social deprivation [42]. Importantly though, epidemiological studies of gene \times lifestyle interactions are often prone to bias and confounding (examples discussed in [43]), which appear to underlie some of the interactions reported in the UK Biobank dataset [42]; this may explain why, in comprehensive analyses of lifestyle intervention trials, little or no evidence of gene \times lifestyle interactions for *FTO* [44] or other obesity loci [45] has emerged (see [46] for detailed discussion of these issues). The major bottlenecks for translating into clinical trials evidence of gene \times lifestyle interactions derived from observational studies, include statistical power (owing to the much smaller sample sizes available in trials and sources of heterogeneity introduced through meta-analysis of diverse trials) and a focus on temporal changes in lifestyle factors instead of cumulative averages of lifestyle exposures (in observational studies this is usually cross-sectionally ascertained BMI, whereas in trials the outcome is usually weight change over months or years).

Meta-analysis of data on $G \times E$ interactions can also lead to the under- or over-estimation of interaction effects. In order to achieve a standardized set of meta-data, meta-analyses often require that key variables within each contributing cohort are reduced to the lowest common form: in trials, this might include collapsing treatment arms (e.g., by combining drug and lifestyle interventions), focusing on the shortest period of follow-up, or by selecting the most rudimentary outcome variables. In $G \times E$ interaction meta-analyses of data from observational studies, the environmental exposure variables are frequently dichotomized, typically by combining two or more categories and comparing this against a referent category or by stratifying continuous variables above and below fairly

arbitrary cut-points to create binary variables. Combining data from multiple cohorts can also increase the variance in the outcome variable, which further reduces statistical power. Furthermore, Winner's curse can lead the marginal and interaction effects generated by a discovery study to be inflated, thereby requiring replication studies to be considerably larger than the primary study. As highlighted above, for *FTO*'s interaction with physical activity, the interaction effect estimate derived from the major replication meta-analysis [44], yielded an interaction effect estimate considerably smaller in magnitude than the discovery study had reported [32]. In combination, these issues can demand that, to be adequately powered, $G \times E$ replication studies are an order of magnitude larger than the original discovery studies [32,37,42,47], which is often unachievable when discoveries are made in large epidemiological cohorts, and replication is sought in clinical trials [46].

Despite the much greater interrogation of how genetic variants, rather than other types of biological variants (e.g., transcripts, epigenomic marks, proteins, metabolites, bacteria) interact with lifestyle, the most compelling evidence that variations in personal biology affect the relationships of food and metabolic health has come from a handful of relatively small studies focused on the gut microbiome. These studies have helped determine that postprandial glycemic responses to specific foods and degree of weight regain after dieting varies from one person to the next and can be predicted at an individual level using biomarker data [3^{••},4,48].

Future key challenges and concluding remarks

Detecting and understanding biomarkers, whether genotypes or other biological variants, that dictate a person's phenotypic responses to lifestyle exposures is being facilitated by major technological developments in biomarker assays and monitoring devices, as well as advances in data processing [49[•]]. As these advances continue, some of the key challenges that have inhibited the detection of gene \times lifestyle interactions in T2D will be overcome.

A significant limitation of many published gene \times lifestyle interaction studies is that the self-report data on diet and physical activity upon which results are based are likely to be biased or confounded. Much of the "objective" data, particularly for physical activity, is also likely to be error-prone (because data are generally collected for relatively short durations and at relatively low resolution) and may be biased (owing to *Hawthorne effect* — i.e., change in a participant's behavior owing to their awareness of being under observation). Thus, there is a need for new technologies that allow unobtrusive assessments of lifestyle and over long durations. The development of popular wearable technologies or mobile

phones that monitor lifestyle [50] is likely to address much of this need; so too may innovations in the use of metabolomics to assess dietary exposures [51**]. Furthermore, the careful integration of these more detailed exposure measures with multi-omics data (epigenomics, transcriptomics, proteomics metabolomics or metagenomics) [52**], is likely to be necessary if we are to understand the complexities of gene \times lifestyle interactions, and translate this knowledge into clinical action. Moreover, the application of cutting-edge technologies to biomaterials from historical cohorts, whilst powerful in many ways, requires the design and implementation of new studies, intended specifically for the investigation of gene \times lifestyle interactions; such studies are likely to include genotype-based recall clinical trials [53].

In summary, there is an extensive body of literature on the interplay of genomics and lifestyle in T2D and related traits. The most compelling evidence comes from studies of gene \times lifestyle interactions in obesity and of microbiome variation in postprandial glycemic response; however, at this time, there is very little compelling data supporting the integration of genetics and lifestyle into the prevention or management of T2D.

Conflict of interest

P.W.F. is a paid consultant for the PREDICT trial and has received funding from diabetes drug companies as part of the Innovative Medicines Initiative of the European Union.

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