

Nutrigenetics: unravelling the genetic contributions to obesity, cardiovascular diseases, and diabetes mellitus

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ABSTRACT

In this review, we aim to explore the field of nutrigenetics and its potential impact on obesity, cardiovascular diseases, and diabetes mellitus. Current dietary approaches in nutritional science often overlook the individual's genetic profile, limiting the effectiveness of personalized diets. Nutrigenetics aims to incorporate genetic data into nutritional interventions to optimize disease prevention and treatment strategies. Regarding obesity, genetic factors, including multiple genes and alleles, influence body weight and predisposition to obesity. The FTO and MC4R genes, for example, have been linked to weight gain and appetite regulation. Similarly, genetic variations in the APO-A and APO-E gene families affect lipid metabolism and susceptibility to cardiovascular diseases. Genetic variations in genes such as MTHFR and PPAR- γ 2 have been associated with increased cardiovascular risk, while dietary factors, such as the consumption of fruits and vegetables, can reduce the likelihood of developing these diseases. In diabetes mellitus, both type 1 and type 2, genetic factors also play a significant role. Genes like IGF2BP2 and PRKAA2 impact insulin resistance and glucose metabolism. Although nutrigenetics is still a developing field, it has the potential to revolutionize personalized nutrition plans and improve health outcomes.

Keywords: genetics, personalized diets, polygenic obesity, nutrigenetics

INTRODUCTION

The field of nutritional science follows a thoroughly documented practice of prescribing specialized diets tailored to individuals belonging to specific groups, such as infants, athletes, or patients with vascular hypertension or mellitus. However, these diets are considered somewhat generalized as they do not take into account the patient's genetic profile [1]. The primary objective of nutritional science should be to prioritize the prevention of disease development and facilitate the crucial repair processes necessary for the treatment of fully developed diseases [2].

The field of genomics encompasses the scientific investigation of complicated conditions, such as type 2 diabetes and cancer, due to the prevailing understanding that these diseases are primarily influenced by a confluence of genetic and environmental factors. The interaction among multiple genes and how they interact exert a more substantial influence on the development and progression of these diseases compared to the isolated effects of individual genes [3,4]. The fundamental principle of nutrigenetics is that each organism possesses a distinct genetic profile that produces varying

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physiological responses in the body based on the bioactive constituents of food, thereby exerting differential effects on nutrient absorption [1]. The topic of exploration pertains to the comprehensive examination of the impact of nutrition on the entirety of an organism’s genetic material, as well as the resulting temporal changes observed in the transcriptomics, proteomics, and metabolomics domains, with the aim of elucidating the observable characteristics of an organism [3].

Although we do not know the exact time nutrigenetics appeared, we know that the concept of food affecting people in different ways has been around since ancient Greece, when the saying “What is food for one is to others bitter poison” was being circulated. In 1945, a team of scientists conducted experiments on W-Swiss mice to investigate the relationship between genes and diets. The mice were conditioned on a diet consisting of whole wheat and whole dried milk. Despite being fed the same food, the experiments revealed variations in the lifespan of the mice, with some dying faster than others. This study is one of the earliest scientific papers documenting the interactions between genes and diets. In 1975, Mulligan RO and Brennan WC [5] introduced the term “nutrigenetics” in

a book focused on the study of individual genetics titled “Nutrigenetics: New Concepts for Relieving Hypoglycemia” [1].

Numerous factors, from the purely economic to the geographical, have a substantial impact on an individual’s nutrition. By creating personalized nutrition plans based on the genetic material of patients who exhibit symptoms of disease or who have already been diagnosed, nutrigenetics can aid in their management or even treatment [6].

The discipline of nutritional science endeavors to enhance health outcomes by recommending customized diets designed for specific populations, including infants, athletes, and individuals with vascular hypertension or mellitus. Nevertheless, the current dietary approaches have been somewhat oversimplified, failing to take into account the unique genetic makeup of each individual. In order to overcome this constraint, the main aim of this article is to investigate the growing discipline of nutrigenetics. This field centers on the intricate relationship between an individual’s genetic makeup and the impact of dietary components on gene expression, metabolism, and health results. The objective of incorporating

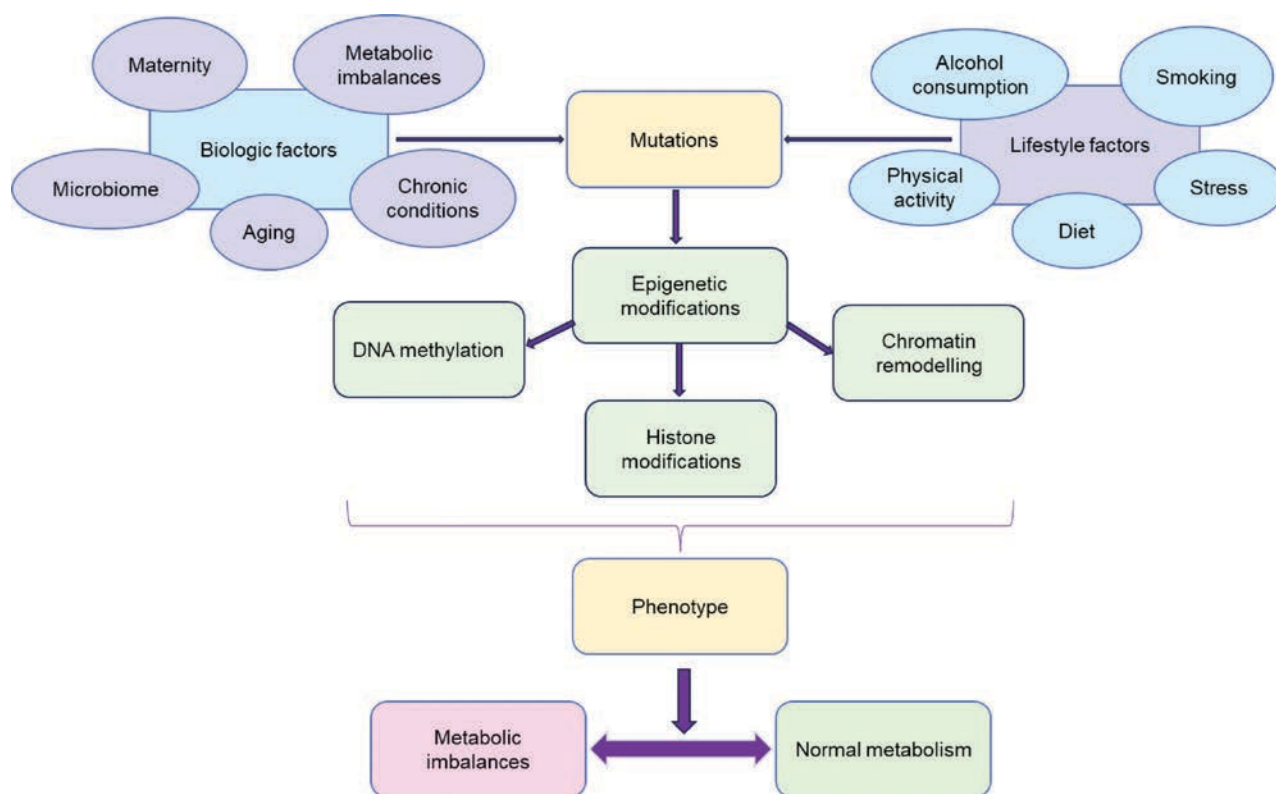


FIGURE 1. The intricate relationship between biological factors, lifestyle factors, and epigenetic modifications in the development of metabolic disorders (Adapted from [7-9])

genetic data into nutritional interventions is to individualize dietary plans and optimize the efficacy of disease prevention and treatment strategies.

NUTRIGENETICS AND OBESITY

The global prevalence of overweight and obesity in adults aged 18 years and older has been increasing in recent decades. Overweight is defined as having a body mass index (BMI) of 25 kg/m² or higher, while obesity is defined as having a BMI of 30 kg/m² or higher [10]. Obesity is an abnormal or excessive quantity of fat that represents a risk for the health and well-being of an individual. It is one of the most prevalent diseases of the last century, with over 4 million people suffering from it. The World Health Organisation (WHO) classifies it as an epidemic, with an estimated 70% of the global population projected to experience the condition or a related disease [6].

From a genetic point of view, obesity can be diagnosed by observing multiple alleles of different genes that each have a small influence over the BMI, which directly determines the weight of an individual [11].

Loos RJF and Bouchard C. [12] proposed a classification system consisting of four levels to describe the genetic influence on obesity: genetic obesity, strong genetic predisposition, slight genetic predisposition, and genetically resistant. Genetic obesity accounts for a significant proportion, approximately 5%, of all reported cases of obesity. Many of these cases are classified as severe, as they persist despite various external and internal factors. Predispositions are influenced by external factors, whereas genetic resistance enables individuals to maintain a normal or near-normal body weight despite the presence of obesogenic conditions [12].

Historically, the clinical management of this ailment has centered on the delicate equilibrium of energy, a methodology that is presently being demonstrated as outdated. It is imperative to address the patient's predisposition and receptiveness to interventions aimed at shedding pounds at the molecular and metabolic planes, encompassing genetic interplays.

Martinez JA and Milargo FI [13] classified genes based on their involvement in genetically regulated mechanisms and processes that contribute to the

maintenance of body weight homeostasis. These processes were: physical activity, appetite regulation, adipocyte differentiation, insulin signaling, mitochondrial function, lipid metabolism, thermogenesis, and energetic effectiveness. The genes were subsequently classified based on the manner in which the metabolic functions are arranged. Within this context, the aforementioned elements were incorporated, encompassing the following components: the genes MC3R (melanocortin 3 receptor), MC4R (melanocortin 4 receptor), POMC (proopiomelanocortin), LEP (leptin), LEPR (leptin receptor), and FTO (fat mass and obesity associated gene) are involved in regulating energy intake. Similarly, the genes PLIN1 (perilipin 1), APOA5 (Apolipoprotein A-5), LIPC (Lipase C, Hepatic Type), and FABP2 (fatty acid-binding protein 2) play a role in lipid metabolism. The genes ADRB1 (adrenoceptor beta 1) and UCP1 (uncoupling protein 1) are responsible for maintaining thermogenesis, while the genes PPAR (peroxisome proliferator-activated receptor), TCF7L2 (transcription factor 7-like 2), and CLOCK (circadian locomotor output cycles kaput) control transcription factors [13].

The FTO gene is found on chromosome 16 and is believed to be connected to the development of obesity. Multiple single nucleotide polymorphisms located within the FTO gene have been observed to be correlated with an elevated BMI and weight [14]. The single nucleotide polymorphism rs9930506 located within the FTO gene consistently exhibits links with BMI, hip circumference, and weight. Specifically, individuals who are homozygous for the less common "G" allele exhibit a BMI that is 1.3 units higher compared to individuals who are homozygous for the more common "A" allele [15].

The MC4R gene is involved in the regulation of eating behaviors and the maintenance of energy balance within the organism. The V103I polymorphism (rs2229616) located in the MC4R gene has been linked to a decreased susceptibility to obesity [16]. Multiple studies have demonstrated a correlation between the presence of the uncommon I103 allele and a reduced BMI as well as a diminished susceptibility to obesity in various ethnic groups, such as Caucasians and East Asians. The I103 allele displayed substantial correlations with various characteristics of the metabolic syndrome, including reduced waist size and lower levels of glycosylated hemoglobin [17].

Due to its importance in nutrition and cardiovascular illnesses and given that mutations in the APO-A gene family, which includes APO-A1, APO-A2, APO-A4, and APO-A5, are linked to obesity and dyslipidemia, the APO-A gene family has undergone substantial research [18]. The APO-A4 S347 allele was previously associated with obesity and elevated waist circumference [19], while variations in the APO-A2 (rs3813627 and rs5082) and APO-A5 (rs662799 and rs3135506) genes have demonstrated connections to various lipid consumption and higher susceptibility to obesity in certain populations [20].

NUTRIGENETICS AND CARDIOVASCULAR DISEASES

Cardiovascular disease (CVD) remains the foremost cause of mortality on a global scale, exhibiting a notable surge in the prevalence of fatalities over the course of the previous decade. Ischemic heart disease and stroke collectively account for a significant proportion of these mortalities. Nevertheless, it is worth noting that there has been a discernible decline in age-standardized mortality rates pertaining to CVD during this corresponding timeframe. In the European context, it is noteworthy that despite the gradual decrease in mortality rates associated with CVD, ischemic heart disease, and stroke since the 1980s, it is still imperative to acknowledge that CVD continues to maintain its status as the predominant cause of mortality within the region. CVD is responsible for an estimated 44% of mortality cases throughout Europe. Within this category, ischemic heart disease represents a substantial proportion of these fatalities. The aforementioned statistics serve to underscore the persistent influence of CVD on mortality rates at both the global and regional levels, thereby accentuating the imperative for sustained attempts in the areas of early detection, treatment, and prevention pertaining to cardiovascular ailments [21].

Over the course of time, numerous interventional studies have provided us with the means to identify and describe factors that are linked to an elevated susceptibility to CVDs. These factors encompass both modifiable and nonmodifiable risk factors. In relation to the modifiable dietary factors associated with CVDs, it is widely acknowledged that specific food products, such as almonds or walnuts, possess the ability to mitigate oxidation biomarkers linked to cardiovascular risk and alter lipid profiles in individuals who are

predisposed to such conditions. Conversely, the consumption of fruits or vegetables has been shown to diminish the likelihood of developing CVDs [22,23].

A multitude of epidemiological studies have provided evidence that the primary contributors to the development of CVDs are individual genetic factors. The genome-wide association study (GWAS) has successfully identified multiple genes and loci that are associated with the development of atherosclerosis. Nevertheless, it is important to acknowledge that the studies mentioned above have consistently indicated that only 30% of the genetic contribution to the disease can be ascribed to the specific alleles that have been identified as being susceptible. This relatively low percentage can primarily be attributed to factors such as gene interaction or the existence of rare variants [11].

The interplay between genetic factors and dietary patterns significantly influences the pathogenesis of CVDs. Extensive research has been conducted on the methylenetetrahydrofolate reductase (MTHFR) gene, which plays a significant role in the metabolism of folate and homocysteine, both of which are associated with CVDs. The MTHFR C677T polymorphism, which involves the substitution of alanine with valine, has been found to be correlated with elevated levels of homocysteine in the blood and an elevated likelihood of developing coronary heart disease and acute coronary syndrome [24,25].

Methionine synthase (MTR) is a significant gene involved in the metabolic pathway of homocysteine. Studies have indicated a correlation between the A2756G polymorphism of this gene and an increased susceptibility to CVDs. Polymorphisms within genes involved in the homocysteine pathway, such as MTHFR and MTR, have been observed to have associations with developing type 2 diabetes and hypertension. These findings emphasize the significance of these genes in the development of vascular complications [26,27].

PPAR- γ 2, which is a member of the PPAR gene family, has a role in the metabolism of both glucose and lipids. The Pro12Ala polymorphism located within the PPAR- γ 2 gene has been found to exhibit a correlation with elevated waist circumference and an augmented susceptibility to CVDs. Intriguingly, Ala-allele carriers, who consume a Mediterranean diet, have longer telomeres, indicating a possible protective effect [28].

Moreover, the APO-A and APO-E gene families play a crucial role in the regulation of plasma lipids. There have been various associations observed between genetic variations in the APO-A and APO-E genes and modifications in lipid levels, as well as an elevated susceptibility to CVDs. The APOA5-1131T>C polymorphism has been found to be linked with increased levels of triglycerides and diminished HDL cholesterol levels, thereby augmenting the susceptibility to CVDs. In the same direction, individuals who carry the APO-E4 allele have an elevated susceptibility to developing coronary artery disease, whereas those who carry the APO-E2 allele demonstrate a reduced risk. The APO-E genotype additionally impacts the degree of response to dietary interventions, including the administration of quercetin supplements [29,30].

The previously mentioned findings underscore the importance of genetic variations in the processes of folate metabolism, lipid regulation, and lipoprotein metabolism in relation to the onset and susceptibility of CVDs. In order to enhance the efficacy and treatment outcomes, it is imperative to consider updating the existing nutritional recommendations. This is because the current recommendations may inadvertently hinder the proper transport of proteins for specific nutrients or impede the enzymatic activity required for the metabolism of certain micronutrients. This particular deficiency has the potential to result in substantial alterations to the ultimate phenotype [11].

NUTRIGENETICS AND DIABETES MELLITUS

The prevalence of diabetes mellitus among adults globally has experienced a significant surge over the past 40 decades, with the number of affected individuals rising from 108 million in 1980 to 463 million in 2019. Approximately 90-95% of these instances correspond to type 2 diabetes. Both type 1 and type 2 diabetes exert significant impacts on the health and socioeconomic aspects of communities [31].

Type 2 diabetes, also known as mellitus, is a pathological condition characterized by a significant burden of both mortality and morbidity. The primary factors contributing to this phenomenon can be attributed to the rise of sedentary lifestyles, the improved availability of food resources, and the

limited adaptability of our genetic composition. However, our genetic structure finds itself in a perpetual struggle to keep up with the fast evolutionary trajectory exhibited by a variety of viral pathogens and afflictions [32]. In accordance with the hypothesis of the “thrifty” gene, it is postulated that specific individuals possess genetic predispositions that facilitate the accumulation of a larger amount of adipose tissue. This particular trait is believed to have played a pivotal role in the survival of hunter-gatherer populations, enabling them to endure and flourish in challenging ecological settings characterized by the limited availability of sustenance and rest. In contemporary times, it has been established through numerous epidemiological experiments that the existence of this gene is intricately implicated in the progression of diabetes [32].

Numerous genetic factors intricately contribute to the complex process of diabetes development and its subsequent progression. Genetic elements such as NFE2 (nuclear factor erythroid 2) and NF-E2L2 (nuclear factor erythroid 2-like 2) play a pivotal role in orchestrating the regulation of antioxidant proteins, thereby conferring a protective effect against the detrimental consequences of oxidative stress. Research conducted on animals has demonstrated that the activation of specific genes, notably NFE2, exhibits the potential to enhance insulin resistance, inhibit overweight and obesity, and block the apoptosis of β -pancreatic cells [33].

The genes IGF2BP2 (insulin-like growth factor 2) and PARP1 (poly ADP-ribose polymerase 1) are directly associated with β -pancreatic cells. The regulation of pancreatic cell activity and resistance to insulin is governed by IGF2BP2, whereas the excessive activity of PARP1 is linked to tissue damage and the deterioration of β cells [34,35].

The PRKAA2 gene, commonly known as AMP-activated protein kinase (AMPK), promotes fatty acid oxidation and thereby suppresses the formation of glucose, cholesterol, and triglycerides. The sirtuin 1 (SIRT1) gene, responsible for regulating the production of glucose in the liver, metabolism of lipids, and sensitivity to insulin, is subject to interaction. The mutual activation of AMPK and SIRT1 is impaired in the presence of hyperglycemia, resulting in a reduction in the expression of both genes [36].

Inflammation and oxidative stress have also been implicated in the pathogenesis of diabetes. The presence of genetic variations in the advanced glycosylation end-product specific receptor protein (AGER) gene, which plays a role in the development of advanced glycation end-products (AGEs), has been linked to a heightened susceptibility to type 2 diabetes. Studies have demonstrated that the suppression of the nuclear factor kappa-B genes (NFKB1 and NFKB2) exhibits a mitigating effect on inflammation and ameliorates hypertension commonly observed in individuals with diabetes. Furthermore, it has been observed that patients with type 2 diabetes exhibit heightened expression of the FTO gene, which has an impact on the metabolism of oxygen and the lipogenesis process [37,38].

Genetic variations in PIK3R1 (phosphoinositide-3-kinase regulatory subunit 1), IRS1 (insulin receptor substrate 1), FFAR1 (free fatty acid receptor 1), HNF4A (hepatocyte nuclear factor-4 alpha), and ENPP1 (ectonucleotide pyrophosphatase/phosphodiesterase 1) exert an impact on insulin signaling and production. These gene sequences play an essential role in the insulin signaling process, the metabolism of glucose, and the secretion of insulin. The presence of genetic variations, specifically within the promoter region of the HNF4A gene, has been linked to a heightened susceptibility to type 2 diabetes [39].

The increasing incidence of type 2 diabetes underscores the need for a deeper understanding of the intricate relationship between genetics and

nutrition. The fields of nutrigenetics and nutrigenomics provide significant insights into the genetic determinants underlying the onset and progression of diabetes, thereby emphasizing the significance of tailored dietary interventions and lifestyle adjustments in the prevention of type 2 diabetes.

CONCLUSIONS

In conclusion, the emerging field of nutrigenetics holds great promise in unravelling the genetic contributions to obesity, cardiovascular diseases, and diabetes mellitus. By incorporating an individual's genetic profile into personalized nutrition plans, nutrigenetics aims to optimize disease prevention and treatment strategies. The genetic basis of obesity has been extensively studied, revealing multiple genes and alleles that influence body weight and predisposition to obesity. Similarly, genetic factors play a significant role in the pathogenesis of cardiovascular diseases, affecting lipid metabolism, homocysteine levels, and response to dietary interventions. In the case of diabetes mellitus, various genes involved in insulin signaling, glucose metabolism, and inflammation have been identified as key players. However, it is important to note that nutrigenetics is still a developing field, with a need for more clinical studies to validate the theoretical findings. Nevertheless, as we continue to discover new genes and unravel their functions, nutrigenetics holds immense potential for guiding personalized dietary interventions and improving health outcomes for individuals with obesity, cardiovascular diseases, and diabetes mellitus.

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