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The relationship between gene-environment interaction in personalized nutrition, disease outcomes and ethical implications

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Abstract: The increasing recognition of the pivotal role of healthy nutrition has prompted a profound exploration into the intricate interplay between genes and dietary patterns. Following the discovery of the human genome map, the conventional understanding of diet's role expanded beyond mere sustenance and adequate nutrition. In recent years, personalized nutrition has emerged as a dynamic and multidimensional field of inquiry, encompassing various facets, including the analysis of dietary patterns, the identification of disease determinants and underlying causes, the intricate interrelationship between genetic factors and one's current health status, legislative considerations, and the promising landscape of innovations poised to revolutionize the field. Personalized nutrition, rooted in genotype-based approaches, seeks to prevent chronic diseases, and enhance overall wellness. This innovative field encompasses two main pillars: nutrigenetics and nutrigenomics. Nutrigenomics further enables the identification of genes influencing physiological responses to diet and the subtle genetic variations, or polymorphisms, that impact crucial nutritional outcomes, while also shedding light on the influence of environmental factors on gene expression. Moreover, it aims to understand gene and diet interactions at the cellular and molecular level and to create nutritional strategies specific to the individual's genome. New findings in nutrition research using genomic techniques will help nutrition researchers and nutritionists to make more personalized recommendations; therefore, it is thought that compliance with dietary recommendations may increase when supported by genomic-based information. The inclusion of personalized nutrition in our health system may help us prevent the onset and progression of diseases. This comprehensive review delves into the multifaceted realm of personalized nutrition, elucidating its potential to reshape future studies and guide the development of tailored nutrition plans. Beyond its current scope, personalized nutrition promises to guide in a paradigm shift in how we approach health and well-being, making it an essential cornerstone in the evolution of healthcare and lifestyle choices. As this evolving situation is explored in more depth, synergies between genes and nutrition will enable improvements in the approach to health and well-being.

Keywords: nutrigenomics, ethics, individual nutrition

Kişiye özel beslenmede gen-çevre etkileşimi, hastalık sonuçları ve etik uygulamalar arasındaki ilişki

Özet: Sağlıklı beslenmenin hayati rolünün giderek daha fazla tanınması, genler ve beslenme kalıpları arasındaki karmaşık etkileşimin derinlemesine araştırılmasına yol açmıştır. İnsan genom haritasının keşfinin ardından, diyetin rolüne ilişkin geleneksel anlayış, sadece beslenme ve yeterli beslenmenin ötesine geçmiştir. Son yıllarda kişiselleştirilmiş beslenme, beslenme kalıplarının analizi, hastalığın belirleyicilerinin ve altta yatan nedenlerin tanımlanması, genetik faktörler ile kişinin mevcut sağlık durumu arasındaki karmaşık ilişkiler, yasal düzenlemeler ve mevzuat gibi çeşitli yönleri kapsayan dinamik ve çok boyutlu bir araştırma alanı olarak ortaya çıkmıştır. Genotip tabanlı yaklaşımlara dayanan kişiselleştirilmiş beslenme, kronik hastalıkları önlemeyi ve genel refahı iyileştirmeyi amaçlamaktadır. Bu yenilikçi alan, nutrigenetik ve nutrigenomic olmak üzere iki ana konuyu kapsamaktadır: Nutrigenomik, diyete fizyolojik tepkileri etkileyen genlerin ve kritik beslenme sonuçlarını etkileyen genetik varyasyonların veya polimorfizmlerin tanımlanmasını sağlarken, aynı zamanda çevresel faktörlerin gen ifadesi üzerindeki etkisine ışık tutar. Ayrıca, hücresel ve moleküler düzeyde gen ve diyet etkileşimlerini anlamayı ve bireyin genomuna özgü beslenme stratejileri oluşturmayı amaçlamaktadır. Genomik teknikler kullanılarak yapılan beslenme araştırmalarındaki yeni bulgular, beslenme konusunda çalışan araştırmacıların ve beslenme uzmanlarının daha fazla kişiselleştirilmiş önerilerde bulunmasına yardımcı olacaktır; bu nedenle, genom tabanlı bilgilerle desteklendiğinde diyet önerilerine uyumun artabileceği düşünülmektedir. Kişiselleştirilmiş beslenmenin sağlık sistemimize dahil edilmesi, hastalıkların başlamasını ve ilerlemesini önlememize yardımcı olabilir. Bu kapsamlı inceleme, kişiselleştirilmiş beslenmenin çok yönlü alanını araştırarak, gelecekteki çalışmaları yeniden şekillendirme ve kişiye özel beslenme planlarının geliştirilmesine rehberlik etme potansiyelini açıklamaktadır. Mevcut kapsamının ötesinde, kişiselleştirilmiş beslenme, sağlık ve esenliğe nasıl yaklaştığımız konusunda bir paradigma değişimine rehberlik etmeyi vaat ediyor ve onu sağlık hizmetleri ve yaşam tarzı seçimlerinin evriminde temel bir köşe taşı haline getiriyor. Gelişen bu durum daha derinlemesine incelendikçe, genler ve beslenme arasındaki sinerji, sağlık ve refah yaklaşımı arasında gelişmeler mümkün olacaktır.

Anahtar Kelimeler: nutrigenomik, etik, kişiselleştirilmiş beslenme.

Review

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1. Introduction

The well-established connection between nutrition and health has long been a focal point of scientific investigation. Historically, research primarily centered on understanding the diseases stemming from malnutrition or the positive impact of specific nutrients on human well-being.

However, a groundbreaking shift occurred with the completion of the Human Genome Project in 2001, catapulting studies in this field into a new dimension. This monumental endeavor had a revolutionary impact on our comprehension of health and nutrition. According to the Human Genome Project's findings, foods wield a profound influence over the intricate process of genetic information transfer from genes to protein synthesis (Ghosh, 2009). It has become increasingly evident that individuals exhibit unique responses to dietary factors due to genetic variants that influence the absorption and metabolism of essential components. Consequently, tailoring dietary recommendations to an individual's genotype holds immense promise in preventing chronic diseases, surpassing the effectiveness of standardized diets.

The recognition of nutrition as a pivotal factor in chronic disease prevention has garnered widespread attention across the globe (Joost et al., 2007). Subsequently, the concept of "personalized nutrition" emerged, built on the premise that dietary adjustments based on an individual's genetic makeup could lead to significant improvements in health outcomes (Gibney et al., 2016).

Personalized nutrition, rooted in genotype-based approaches, seeks to prevent chronic diseases, and enhance overall wellness (Ferguson et al., 2016). This innovative field encompasses two main pillars: nutrigenetics and nutrigenomics (Gaboon, 2011). "Nutrigenetics" involves deciphering an individual's genetic code and polymorphisms to personalize dietary recommendations. By leveraging this genetic information, personalized nutrition can also aid in early disease detection (San-Cristobal et al., 2013). In tandem, "nutrigenomics" utilizes omic technologies to unravel the intricate interplay between nutrients and genes, providing a deeper understanding of the nutrient-gene relationships essential for optimizing health and preventing potential diseases (Fenech et al., 2011). Nutrigenomics further enables the identification of genes influencing physiological responses to diet and the subtle genetic variations, or "polymorphisms," that impact crucial nutritional outcomes, while also shedding light on the influence of environmental factors on gene expression (Gaboon, 2011). Nutrigenetics describes how genes determine the effects that nutrients have on the body; nutrigenomics describes how the foods change how genes are expressed (Rajasekaran & Davison, 2023). In other words, it aims to understand gene and diet interactions at the cellular and molecular level and to create nutritional strategies specific to the individual's genome (Ahluwalia, 2021). Both nutrigenomics and nutrigenetics investigate the relationships between nutrition, metabolism, and genetic mechanisms. The main aim is to identify food-related health traits and nutrition-related diseases. Another essential area related to these sciences aims to evaluate the composition and quality of foods by studying proteomics and metabolic pathways (Bahinipati et al., 2021).

Within the realm of personalized nutrition, nutrigenomic-based dietary plans are tailored to individual gene sequences, transcending factors such as age, gender, body mass index, diet, physical activity, and health status, in the quest to combat obesity and various diseases (Poinhos et al., 2014).

It's crucial to acknowledge that nutrigenetics and nutrigenomics are influenced by a myriad of factors, including variations in food bioavailability, metabolism among individuals, food preferences, cultural and economic factors, geographical influences, and personal taste perceptions (Fenech et al., 2011). Therefore, gene-based personalized nutrition aims to integrate an individual's genetic, phenotypic, and health-related information to provide precise dietary guidance to improve or optimize health status (Rajasekaran & Davison, 2023).

Additionally, malnutrition can exert an impact on gene expression and genome stability, potentially leading to abnormal gene dosage and adverse phenotypic outcomes. Beyond nutrition, the field of "pharmacogenomics" explores the intricate relationship between genetic variations and individual responses to drug metabolism (Coşkun, 2007).

2. Gene and Diet Interactions

In recent years, the exploration of gene-diet interactions has gained substantial traction within the scientific community, as researchers strive to elucidate the intricate interplay between genetic variations and dietary components. Genomics technologies can be used to study the relationship between the human genome, nutrition, and health. For example, food components can interact with genes and their expression to alter phenotypes. Consequently, genes can influence absorption, metabolism, or transport of food nutrients or its site of action and thus influence the overall response to the diet (Rudkowska, 2021). This area of study holds immense potential for unraveling the mechanisms through which personalized nutrition can influence disease risk by modulating metabolic pathways. Genomics technologies can improve the understanding of the relevant metabolic pathways to the risk of diseases and the responses to diet. Such genomics data can facilitate the development of personalized nutrition recommendations.

A diverse array of research efforts has been directed towards understanding these interactions, yielding valuable insights that have the potential to reshape our approach to disease prevention and management. Research findings demonstrate that some individuals may respond differently to nutrition recommendations and thus may benefit from other dietary recommendations (Rudkowska, 2021). This section provides a comprehensive review of studies conducted on gene-diet interactions, organized under distinct headings that highlight their respective contributions.

2.1. Single nucleotide polymorphisms

Single nucleotide polymorphisms, commonly referred to as SNPs, are the most prevalent type of genetic variation found in human DNA. They are essentially single-letter changes in the DNA sequence, where one nucleotide (adenine, thymine, cytosine, or guanine) is replaced by another at a specific position in the genome.

Within the human population, SNPs abound, with millions of SNP sites scattered throughout the human genome. Typically, a SNP locus harbors two different alleles. While some SNPs are exclusive to specific human populations, many are polymorphic and shared across diverse ethnic groups. SNPs are a hallmark of genetic variation in the modern molecular age, denoting instances where two different nucleotides occupy a given position on a chromosome (Daiger et al., 2014).

The integration of genotypic information into nutritional approaches, alongside traditional phenotypic considerations, holds substantial promise in combatting diseases and obesity. For instance, nutrigenetic insights, particularly those related to SNPs, play a pivotal role in designing tailored weight loss interventions, which inherently involve multiple genes. SNPs, along with other genetic variations like copy number variations, nucleotide repeats, insertions, deletions, and telomere length, collectively contribute to the diversity of individual responses to dietary interventions (Martinez & Milagro, 2015). Additionally, they offer a means to address diseases that typically manifest in adulthood, enabling personalized dietary responses guided by the epigenetic modifications acquired over time (Cotton & Murray, 2016).

Specific genetic polymorphisms in humans exert distinct effects on responses to dietary regimens. Each gene serves as a blueprint for the synthesis of proteins, the building blocks of tissues that orchestrate essential biological functions. Variations in SNPs introduce alterations to this blueprint, resulting in the synthesis of varying protein quantities or modified protein structures (Gaboon, 2011).

These genetic polymorphisms wield significant influence over how the body absorbs and metabolizes dietary components. Furthermore, epigenetic events, such as changes in DNA methylation patterns, can modulate gene expression, leading to variable responses to dietary constituents (Gaboon, 2011). Consequently, understanding and considering these genetic and epigenetic factors are integral to crafting personalized dietary recommendations that account for individual variations in metabolism and health outcomes.

SNPs play a crucial role in the field of personalized nutrition. Genetic variations in SNPs can influence an individual's response to dietary components and nutrients. These variations can affect how nutrients are metabolized, absorbed, and utilized by the body, potentially impacting an individual's nutritional requirements and disease susceptibility.

For instance, certain SNPs may affect an individual's ability to metabolize specific vitamins, such as folate or vitamin D, leading to variations in nutrient requirements. Additionally, SNPs related to taste receptors or metabolism can influence an individual's food preferences and how they respond to different diets.

Researchers and practitioners in the field of personalized nutrition use information about an individual's SNPs to tailor dietary recommendations. By considering an individual's genetic makeup, along with other factors like lifestyle and health status, personalized nutrition strategies can be designed to optimize health outcomes, prevent disease, and improve overall well-being.

In conclusion, SNPs are a fundamental form of genetic variation that underpins the diversity observed within human populations. Their role in influencing traits, disease susceptibilities, and responses to dietary factors makes them a crucial consideration in the burgeoning field of personalized nutrition. Understanding the implications of SNPs and their interactions with diet holds promise for the development of more effective and tailored approaches to promoting individual health.

2.2. Lactose intolerance

Lactose intolerance stands out as a compelling example of how SNPs can dramatically alter gene expression and individuals' responses to specific nutrients. Genetic variations play a crucial role in determining an individual's ability to digest lactose, the sugar found in milk and dairy products. Notably, lactose intolerance is relatively uncommon in Northern European populations but is more prevalent in Asia and parts of Europe. This disparity is attributed to genetic differences related to lactase persistence, an enzyme responsible for lactose digestion. In most mammals, including humans, the gene responsible for lactase persistence becomes inactivated after the weaning period (Coşkun, 2007).

2.3. Folate deficiency

Folate, derived from vitamin B9, primarily found in green vegetables such as broccoli and Brussels sprouts, serves as an illuminating case study highlighting the profound impact of dietary choices on genetic outcomes. Folate plays a pivotal role in DNA synthesis, a fundamental process in the body. Inadequate folate levels can heighten the risk of cancer by rendering DNA strands more susceptible to damage. Folate assumes particular importance during fetal development when DNA synthesis rates soar due to rapid cell division and growth. Additionally, folate contributes significantly to the development of the baby's spinal cord, making it imperative for pregnant women to ensure sufficient intake, often through folic acid supplements (NIH, 2022).

Maintaining adequate folate levels is critical for preventing several chronic diseases. Inadequate folate intake can lead to elevated blood homocysteine levels, which, in turn, increases the risk of cardiovascular diseases. Furthermore, insufficient folate intake can disrupt DNA synthesis and methylation, potentially contributing to cancer development. It's worth noting that while folate has many positive effects, some studies suggest it might accelerate the progression of existing tumors. Central to folate metabolism is the enzyme methylenetetrahydrofolate reductase (MTHFR), which plays a pivotal role. The MTHFR 677C/T polymorphism is a SNP that can impair the activity of this enzyme. Consequently, individuals with a homozygous genotype for the MTHFR 677C/T polymorphism may face an increased risk of cancer when exposed to low levels of folate (Cahill & El-Sohemy, 2011).

Numerous studies have linked folate deficiency to the incidence of colorectal cancer. Folate's impact on DNA stability can be explained through two primary mechanisms. First, it facilitates the conversion of uracil to thymine by donating a methyl group, which is vital for DNA synthesis and repair. However, when folate is insufficient, imbalances occur in the DNA pool, leading to incorrect uracil binding to DNA. This misbinding can result in chromosomal damage and increase the risk of cancer. There is also evidence suggesting that folate can modulate DNA synthesis and repair by altering gene expression in vitro. Nevertheless, when studying the effects of nutrient-gene interactions in humans, researchers must exercise caution, given the complexities of folate metabolism and the influence of polymorphisms in key enzyme systems, particularly in comparisons with findings from animal studies on rodents (Duthie et al., 2002; Abbasi et al., 2018).

2.4. Phenylketonuria

Phenylketonuria (PKU) serves as a compelling illustration of gene-diet interactions. Individuals afflicted with this condition must carefully manage their diets by avoiding foods rich in the amino acid phenylalanine, found in dairy products, meat, fish, poultry, eggs, legumes, nuts, and artificial sweeteners. PKU is influenced by over 500 known genetic mutations, each of which can lead to mild or severe phenotypic changes. Early PKU testing in newborns and the swift initiation of dietary therapy are essential measures to prevent mental retardation associated with the condition (Singh et al., 2008).

Phenylalanine is metabolized into the amino acid tyrosine within the body. However, individuals lacking the phenylalanine hydroxylase enzyme experience a conversion of phenylalanine into phenylpyruvic acid instead of tyrosine. This accumulation can disrupt brain development, leading to intellectual disabilities and seizures. Therefore, individuals with PKU must adhere to low-phenylalanine diets (Köseoğlu & Çelikel, 2020).

Leveraging personalized genetic information in the context of personalized nutrition studies has demonstrated efficacy in tailoring nutrition plans for individuals with PKU (Görman, 2006). While dietary therapy for PKU was developed six decades ago and its fundamental principles remain applicable today, several aspects of dietary therapy remain insufficiently explored. Variations exist in the composition of essential and non-essential amino acids per 100 grams in different phenylalanine-free amino acid formulations. Some studies suggest potential micronutrient excesses in amino acid formulations lacking iron, underscoring the need for further research to refine nutrient composition. Additionally, limited data exist in the literature regarding lifelong phenylalanine

tolerance and the nutritional management of PKU patients undergoing dietary therapy (MacDonald et al., 2011).

2.5. High-fat nutrition

Long-term consumption of high-fat diets is associated with various adverse health outcomes, including obesity, insulin resistance, and cardiovascular diseases. High-fat nutrition significantly impacts the expression of metabolic genes in the liver and adipose tissue, influenced by hypothalamic expression and the consequences of neuropeptides and energy metabolism (Lindroth et al., 2015).

Genes encoding apolipoproteins A-I and A-II (APOA1 and APOA2) play a pivotal role in lipid metabolism. Recent research has explored the relationship between saturated fat consumption and body mass index concerning a common functional APOA2 polymorphism. The prevalence of the CC genotype ranged from 10.5% to 16.2% in three populations, with individuals possessing the CC genotype experiencing approximately twice the obesity risk with low saturated fat intake compared to T allele carriers. However, this relationship was not observed in the low saturated fat group. This study underscores the significance of dietary-gene interactions, particularly within the realm of nutrigenomics (Cahill & El-Sohemy, 2011).

Animal studies have demonstrated that long-term high-fat nutrition induces DNA methylation changes in genes such as melanocortin receptor 4 (MC4R) in the brain and leptin (LEP) in adipose tissue. High-fat diets can alter the expression of various subsets of histone deacetylases (HDACs), including HDAC5 and HDAC8, within the hypothalamus. These dietary influences on gene expression occur through epigenetic modifications in tissues (Lindroth et al., 2015).

High-fat nutrition during developmental periods can have enduring effects on metabolic health. Animal studies have shown that maternal high-fat nutrition during pregnancy and lactation can lead to obesity, altered lipogenic expression, and a heightened risk of obesity passed on to subsequent generations. Thus, high-fat nutrition has a far-reaching impact on metabolic health worldwide (Lindroth et al., 2015).

High-density lipoprotein (HDL) cholesterol plays a pivotal role in preventing cardiometabolic disorders, thanks to its potential protective effect. An inverse relationship exists between HDL cholesterol levels and cardiovascular diseases. Both environmental and genetic factors influence HDL concentrations, with dietary fat interactions affecting these genetic polymorphisms and their impact on HDL cholesterol levels (Cahill & El-Sohemy, 2011).

While the global effects of high-fat nutrition on epigenetic modifications are not yet fully understood, there is an emerging body of research focused on identifying biomarkers that can monitor epigenetic changes in parental reproductive cells in response to high-fat nutrition (Lindroth et al., 2015).

3. Modelling Personalized Nutrition and Its Association with Specific Diseases

Gene-diet interactions can contribute to epigenetic changes that affect basic biological processes, including nutrient metabolism. Epigenetics refers to the change in the readability or expression of genes due to environmental influences and their reflection on the phenotype, without changing the DNA code itself. Modulation and regulation of gene expression occur as a result of positive or negative reflections of epigenomic changes on DNA. Both positive and negative epigenetic changes develop when individuals are exposed to various nutrient deficiencies and their reflection on the phenotype can leave a mark on genes passed from one generation to the next. Epigenetic changes explain that what we eat can not only be used for nutrition but also change body system functions. Our genetic diversity can affect epigenetic changes. Gene-based personalized nutrition applications refer to personalized nutrition treatments based on the integration of information such as a person's life stage, dietary history, anthropometry, biomarkers, family history, food preferences and health status with their genetic genome. In this way, genome integrity can be preserved, and diseases can be prevented (Rajasekaran & Davison, 2023).

An individual's state of health is primarily shaped by a complex interplay of environmental exposures, dietary choices, lifestyle factors, and inherited genetic traits. Effective interventions for addressing an individual's health and managing disease necessitate a personalized approach that considers the unique circumstances, health trajectory, and functional variations of each person. The essence of personalized nutrition lies in its ability to create targeted, preventive, and therapeutic strategies that can fully optimize an individual's well-being possible. This modeling framework encompasses four key phases: (1) assessment, (2) interpretation, (3) intervention, and (4) ongoing monitoring and evaluation (Bush et al., 2019).

During the assessment phase, both qualitative and quantitative data are gathered about the individual, providing a comprehensive understanding of their health profile. In the interpretation stage, specialists construct a roadmap that delineates the functioning or dysfunction of the individual's body systems and the intricate relationships among biochemical pathways. This personalized roadmap guides the personalized nutritionist in identifying the root causes of existing health issues and devising the necessary interventions, education, counseling, and continuous care services.

The ongoing monitoring and evaluation phase play a pivotal role in assessing the effectiveness of the previously established roadmap, ensuring the achievement of desired outcomes, and refining the approach as needed. This iterative process is essential for obtaining optimal results and maintaining the sustainability of the model. Additionally, it allows experts to collect qualitative and quantitative data pertaining to the individual's evolving health status. The modeling of personalized nutrition is given in Figure 1 (Bush et al., 2019).

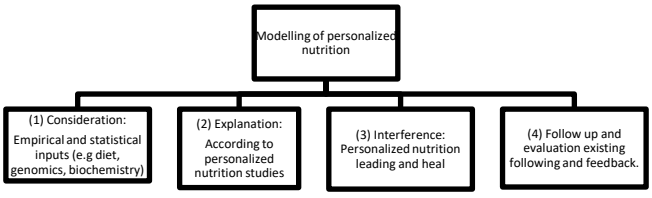

Figure 1. The modelling of personalized nutrition.
Şekil 1. Kişiye özel beslenme modeli.

The Personalized Nutrition Maintenance Model should be conducted in periodic intervals, with continuous development of applications until the desired outcomes are attained. Research in the realm of personalized nutrition plays a pivotal role in enhancing our understanding of how genetic, phenotypic, biochemical, and nutritional data collectively influence an individual's health. At its core, the personalized care model stands as the cornerstone of this clinical approach.

3.1. Obesity and its relationship with personalized nutrition

Obesity is characterized by the abnormal accumulation of body fat, accounting for more than 20% of an individual's total weight. It considers factors such as height, age, and muscle

development when determining healthy body weight. Obesity is typically diagnosed through the calculation of an individual's body mass index (BMI), with a threshold of 30 kg/m² set by national health organizations. Despite numerous warnings from the World Health Organization, the prevalence of obesity continues to rise, especially among children and adults. Sadly, obesity is often underestimated by the public, yet it poses a significant risk of diseases, disability, and even premature death (Zhong et al., 2016).

Research conducted through genome-wide association studies has identified many known obesity-related genes. Recent advances in genomics have enabled the identification of interactions between genetic variation and dietary factors in association with obesity and weight change. Data from studies such as epigenomics and metabolomics suggest that more complex interactions between global human body characteristics and dietary factors may exist at multiple levels in influencing the susceptibility of individuals to obesity (Gasmi et al., 2021).

Key to controlling food intake is the leptin-melanocortin signaling pathway, with over 600 genes and chromosomal regions associated with body weight and composition, culminating in genetic risk accumulation that elevates the likelihood of obesity. Notably, four genes play prominent roles: Fat mass and obesity-associated (FTO), fatty acid-binding protein 2 (FABP2), LEP, and MC4R. The FTO gene governs preferences like satiety, dairy consumption, and overeating, playing a part in nutrient absorption. The FABP2 gene facilitates the intracellular transport and metabolism of dietary fatty acids and their acyl-CoA esters, aiding in stabilizing appetite and preventing small intestine-related issues. The LEP gene influences food and energy consumption by balancing metabolism and physical activity. Finally, the MC4R gene stands as a pivotal regulator of food intake and energy expenditure equilibrium (Maculewicz et al., 2022).

A recent study (Kettunen et al., 2012) found that a SNP rs1440581 near the PPM1K gene (PP2C domain-containing protein phosphatase 1K) was associated with serum BCAAs and AAAs, which are associated with the risk of obesity and diabetes (Wang et al., 2011; McCormack et al., 2013). Furthermore, PPM1K has been identified as a susceptibility gene for type 2 diabetes (Taneera et al., 2012). Another research (Xu et al., 2013) genotyped the PPM1K SNP rs1440581 and reported that dietary fat significantly modifies genetic effects on changes in body weight, fasting insulin, and insulin resistance. It was hypothesized that individuals carrying the C allele of the PPM1K SNP rs1440581 may benefit less from weight loss and improved insulin sensitivity when on an energy-restricted high-fat diet than those without this allele. These studies would provide support for the beneficial effects of personalized dietary planning in the prevention and treatment of obesity and related disorders.

3.2. Type-2 diabetes mellitus and its connection to personalized nutrition

Type-2 diabetes mellitus (T2DM) can result from either insufficient insulin production or the body's reduced responsiveness to insulin. It's identified by elevated blood sugar levels, known as 'hyperglycemia,' as well as 'dyslipidemia.' In Western nations, T2DM prevalence is alarmingly high, often attributed to excessive food consumption and sedentary lifestyles. However, T2DM is influenced not only by lifestyle factors but also by a complex interplay of environmental and genetic elements. Recent studies in mice have revealed genetic modifications affecting lipid metabolism, highlighting the role of lipids in T2DM. Additionally, various susceptibility genes, regulating lipid metabolism and insulin sensitivity, contribute to the risk of T2DM. Genes like peroxisome proliferator-activated receptor gamma pathway (PPAR-γ) and IRS-1 are of particular significance. PPAR-γ, part of the 'peroxisome proliferator-activated receptor gamma pathway,' plays a crucial role in lipid and carbohydrate utilization; disruptions in this pathway can lead to T2DM. Research is ongoing to investigate drugs and substances targeting this pathway for T2DM prevention and treatment. On the other hand, IRS1, known as 'insulin receptor substrate 1,' encodes a protein phosphorylated by insulin receptor tyrosine kinase. Mutations in IRS1 can lead to insulin resistance (NIH, 2023).

Personalized nutritional therapy for T2DM often involves carbohydrate counting to achieve optimal glycemic control. Carbohydrates should be distributed consistently across meals and snacks, with a daily intake of no less than 130 grams. Protein intake can be categorized as low or high, with a low protein diet helping to reduce glomerular pressure and preserve kidney function, while a high protein diet may exacerbate glomerular damage. Patients with diabetic nephropathy should limit their protein intake to around 0.6-0.8 grams per kilogram of body weight. Regarding fat consumption, the diet should consist of no less than 7% saturated fat of total calorie intake, with trans-fat and polyunsaturated fat making up less than 10%. Cholesterol intake should not exceed 200 mg per day (Gellar & Nansel, 2007).

One study explored the impact of fruit and vegetable consumption on the incidence of T2DM. The results indicated that increasing the consumption of green leafy vegetables reduced the risk of T2DM by 14%. However, increasing the overall intake of fruits and vegetables did not significantly affect the risk of developing T2DM (Carter et al., 2010).

3.3. Cardiovascular diseases and their association with personalized nutrition

Cardiovascular diseases (CVD) represent a complex interplay of dietary habits and chronic disorders, often manifesting through factors such as atherosclerosis, hypertension, and thrombosis. Both environmental influences, including diet, and genetic factors play significant roles in these CVD risk factors. Additionally, obesity stands out as a major contributor to CVD risk, as polymorphic genes can exert positive or negative influences on energy balance control, subsequently affecting the development of CVD (Gaboon, 2011).

Atherosclerosis, characterized by the thickening of arterial walls due to the accumulation of fat, calcium, and cholesterol, is a primary contributor to CVD. It arises from the convergence of lipid transport, metabolic disturbances, and chronic inflammation. Apolipoprotein-encoding genes introduce genetic variations, influencing susceptibility to CVD and responses to dietary interventions. Consequently, specific changes can impact the effectiveness of certain enzymes and hormones in the context of CVD or dietary modifications (Gaboon, 2011). Factors contributing to cardiovascular diseases include modifiable ones like obesity, diabetes, hypertension, and dyslipidemia, as well as non-modifiable factors such as genetics, age, and sex (Juma et al., 2014).

3.4. Hypertension and its connection to personalized nutrition

Hypertension, often defined as elevated blood pressure levels within arterial vessels, exerts excessive force on the walls of these vessels (Carlberg et al., 2016). Furthermore, studies indicate that the number of individuals with hypertension is projected to rise by 60% by 2025 (Lago et al., 2007). The most common form of hypertension, accounting for 90-95% of all cases, results from a combination of environmental factors and specific genetic links. This type of hypertension is closely associated with atherosclerosis, increasing the risk of stroke, CVD, and renal failure due to changes in blood volume regulated by renal salt stability. The relationship between

hypertension formation and salt intake can be understood within an evolutionary context. In the past, low-salt diets were common in Sub-Saharan Africa, where early human civilizations originated, leading to a conservation of salt and water in the body. However, as populations migrated to Europe and adopted salt-rich diets, hypertension rates increased. Additionally, individuals who are obese face a fivefold higher risk of hypertension than those with a normal weight. Those with a BMI exceeding 25 may experience an 85% higher risk of hypertension. To mitigate hypertension risk, recommendations include reducing salt intake, adopting a low-fat diet, engaging in regular exercise, and moderating alcohol consumption (Carlberg et al., 2016).

3.5. Cancer and Its relation to personalized nutrition

WHO (2022) is described cancer as a life-threatening disease characterized by abnormal cell growth with the potential to invade or metastasize to other organs, is influenced by factors such as age, smoking, poor dietary choices, and unfavourable living conditions. Genetic and environmental factors interact to affect cancer risk. Studies have shown that identical twins have a shared cancer risk of less than 10%, indicating the substantial influence of environmental factors. Foods and their constituents are sources of polymorphisms that can influence carcinogenic metabolism, altering the potential for interactions with target cells and the onset of cancer. Changes related to hormones, which play a central role in hormone-dependent cancers such as breast, prostate, and ovarian cancers, can also be influenced by dietary factors. For instance, phytoestrogens, which are processed similarly to sex hormones, may serve as anti-carcinogenic agents. Additionally, obesity plays a crucial role in hormone regulation (Sung et al., 2021).

Nutrigenetic and nutrigenomic studies have revealed that genes respond to specific nutrients. For example, MTHFR has a significant impact on folate intake, while alpha-1,2-L-fucosyltransferase (FUT2) is linked to B12 vitamin intake. These genes may mediate cancer prevention or treatment through gene-diet interactions, although current research is still in need of further insights (Taylor et al., 2019).

3.6. Psychological disorders and their relationship with personalized nutrition

Nutrigenomics plays a pivotal role in understanding the dynamics of psychological disorders. Analyzing key genes associated with various psychological conditions and their interaction with specific nutrients has led to valuable insights. It is now clear that nutritional imbalances can exacerbate psychological distress. For example, research has shown that conditions like anxiety, obsessive-compulsive disorder and depression may be linked to nutritional deficiencies (Gyorkos et al., 2019).

Depression is a prevalent mental disorder, affecting approximately 280 million individuals globally (WHO, 2021). Genes implicated in depression and anxiety disorders, such as SLC6A4 encoding 5HTT, play a significant role in serotonergic neurotransmission and regulate serotonin levels in synaptic clefts and extracellular sites (Lam et al., 2018).

In the context of anxiety and mental disorders, it is known that foods rich in antioxidants can elevate levels of brain-derived neurotrophic factor (BDNF), which is involved in glucose and energy metabolism regulation and helps prevent β cell exhaustion (Wicinski et al., 2019). Another pivotal gene related to anxiety and mood disorders is monoamine oxidase A (MAOA). The MAOA gene encodes the MAOA enzyme, which is responsible for the breakdown of neurotransmitters like serotonin, norepinephrine, epinephrine, and dopamine. These neurotransmitters are associated with mood regulation, sleep, emotions, stress response, and signal transmission in the brain (Marzo et al., 2022).

Schizophrenia presents another dimension of this topic. A protein known as AKT1, a serine/threonine protein kinase, plays a significant role in schizophrenia by affecting protein expression in the brains of schizophrenia patients (Emamian, 2012). Furthermore, factors such as vitamin B3 and B6 deficiency, mineral deficiencies (especially zinc), and cerebral reactions can contribute to schizophrenia. The recommended treatment involves a balanced diet rich in vitamins and minerals, with an emphasis on foods known to reduce psychosis (Brown & Roffman, 2014).

4. Ethical and Legal Considerations in Personalized Nutrition

The ethical, legal, and social implications of nutrigenomics and human genetic testing have been closely intertwined with the National Human Genome Research Institute (NHGRI) and the Human Genome Project since their inception. With the discovery of genetics, the ability to obtain predictive information about individuals has grown significantly, bringing with it various legal implications. Managing this wealth of knowledge in clinical and research settings is crucial to safeguard individuals' privacy and rights. To protect patients' privacy, a legal framework has been established, providing added protection. In Europe, specific "nutrigenetic" legislation exists in all countries. The World Medical Association's declaration of patients' rights includes the right to confidentiality, the right to information, the right to genetic counseling, and the right to freedom of choice. EIT Food, a scientific research initiative, addresses broader issues arising from genomics research, striving to assist scientists in navigating these challenges in real-time (EIT Food, 2020).

Here are some key ethical and legal considerations associated with personalized nutrition.

4.1. Genetic privacy and data security

Legal approaches to personalized nutrition are constrained by data storage security and personal data access rights. Laws like the Genetic Information Non-discrimination Act (GINA) have emerged to protect individuals from discrimination by insurers and employers. GINA ensures that individuals can undergo medically beneficial genetic tests without fear of losing insurance coverage or employment. It also provides reassurance to research study participants that their DNA will not be used against them. This legislation applies to health plans of all sizes, from employer-based insurance to government-run programs and individual health policies (Ordovas et al., 2018). Striking a balance between data sharing for research purposes and maintaining individual confidentiality is crucial.

4.2. Informed consent and autonomy

Gathering genetic data and personal health information for personalized nutrition requires informed consent. Individuals should fully understand the implications of sharing their genetic data, the potential benefits, risks, and how their data will be used. Not everyone can interpret genetic information equally, and people may react differently to recommendations. Transparent communication ensures individuals can make informed decisions and exercise their autonomy (Mullins et al., 2020).

4.3. Equity and accessibility

Personalized nutrition has the potential to exacerbate health disparities if access to these services is limited by socioeconomic factors. Ensuring equitable access to personalized nutrition services and interventions is essential to prevent privileged populations from benefiting disproportionately (Khoury, 2020).

4.4. Commercialization and marketing

The commercialization of personalized nutrition introduces concerns about profit-driven motives and the potential for exaggerated claims. Ethical guidelines must regulate marketing practices to ensure that promises made about the benefits of personalized nutrition are evidence-based and transparent (Verma et al., 2018).

4.5. Validity and accuracy of recommendations

The accuracy and reliability of personalized nutrition recommendations depend on the quality of genetic and health data, as well as the models used. Ensuring that these recommendations are based on sound scientific evidence is essential to avoid misleading individuals and potentially causing harm (Verma et al., 2018).

4.6. Psychological and emotional impact

Receiving personalized genetic information, especially related to disease risk, can have psychological and emotional implications. Ethical considerations include providing appropriate counseling and support for individuals who may experience anxiety or distress due to their genetic results (Oliveri et al., 2017).

4.7. Consent for secondary use of data

As personalized nutrition databases grow, there's potential for secondary use of data for research beyond the original purpose. Ensuring that individuals' consent covers potential future uses of their data, while respecting their autonomy, is a critical ethical consideration (Nordström & Goosens, 2016).

4.8. Regulation and standards

Establishing clear regulations and standards for personalized nutrition practices is essential to maintain quality, accuracy, and ethical integrity. This includes oversight of genetic testing companies, data handling practices, and the validity of genetic interpretations (Berciano et al., 2022).

4.9. Cultural and societal considerations

Dietary practices often hold cultural and societal significance. Tailoring nutrition recommendations must respect cultural preferences and beliefs while avoiding undue influence or imposition of certain dietary norms (Sunil, 2020).

4.10. Long-term effects and unintended consequences

The long-term effects of personalized nutrition interventions are not always well understood. Ethical considerations include monitoring individuals' health outcomes over time and addressing any unintended consequences that may arise from personalized recommendations.

Navigating the ethical and legal landscape of personalized nutrition requires collaboration among researchers, healthcare professionals, policymakers, ethicists, and individuals. It is essential to strike a balance between promoting innovation and safeguarding individuals' rights, autonomy, and well-being in this transformative field (Verma et al., 2018).

5. The Future of Personalized Nutrition

The future of personalized nutrition holds tremendous promise as it delves into the intricate relationship between genes, diet, and the environment. However, to fully unlock its potential, further research and exploration are imperative, as the current knowledge base does not sufficiently cater to all populations. The challenges facing personalized nutrition can be attributed to three primary factors. First, understanding the connection between individual profiles and dietary interventions requires more time and extensive research. Second, the molecular and physiological processes involved are highly complex and challenging to decipher comprehensively. Lastly, it demands innovative study designs and analytical methods, moving beyond traditional or obsolete techniques for data collection and interpretation (Braconi et al., 2019).

In the coming years, personalized nutrition is poised to expand significantly through the integration of "omic" technologies and machine learning. Omic technologies will advance by phenotyping individuals using nutrigenomics, neuroproteomics, and nutrimetabolomics to establish "biomarker" signatures. These biomarkers will be instrumental in tailoring interventions and diets to suit individual needs and characterizing pathological conditions. However, it is essential to acknowledge that our current knowledge of these complex diseases remains limited. Additionally, advancements in biotechnology and health sciences will yield essential data that can be harnessed through machine learning and data mining techniques. Combining omic technologies, data mining, and machine learning will pave the way for groundbreaking research on a broader scale, potentially at the public level (Braconi et al., 2019).

Addressing the ethical concerns of individuals regarding scientific applications, data management, research practices, development, and product services is paramount. This will have a profound impact on healthcare companies, professionals, relevant organizations, governments, and the public in terms of responsible data usage and safeguarding against potential harm (Castle, 2007).

6. Conclusion

The advent of personalized nutrition, rooted in the understanding of the human genome's role in dietary responses and nutrient-gene interactions, marks a significant milestone in nutrition science. Despite the promising developments in this field, ethical issues surrounding the acquisition, storage, sharing, and interpretation of individual genomic information remain contentious. It is essential for ethical and legal considerations to keep pace with the evolving landscape of personalized nutrition, ensuring that laws and regulations align with the latest developments and protect the rights and privacy of individuals involved in this emerging field.

7. Author Contributions

Study was designed by Nese Sahin Yesilçubuk (NSY). Data collection led by Birsen Demirel (BD). Data analysis and interpretation led by Asli Pinar Kemer (APK) and Batuhan Inanlar (BI) with input from NSY and BD. Manuscript writing led by BI and APK with input from all authors. All authors read and approved the final manuscript.

8. Conflict of Interest

There is no conflict of interest.

9. References

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