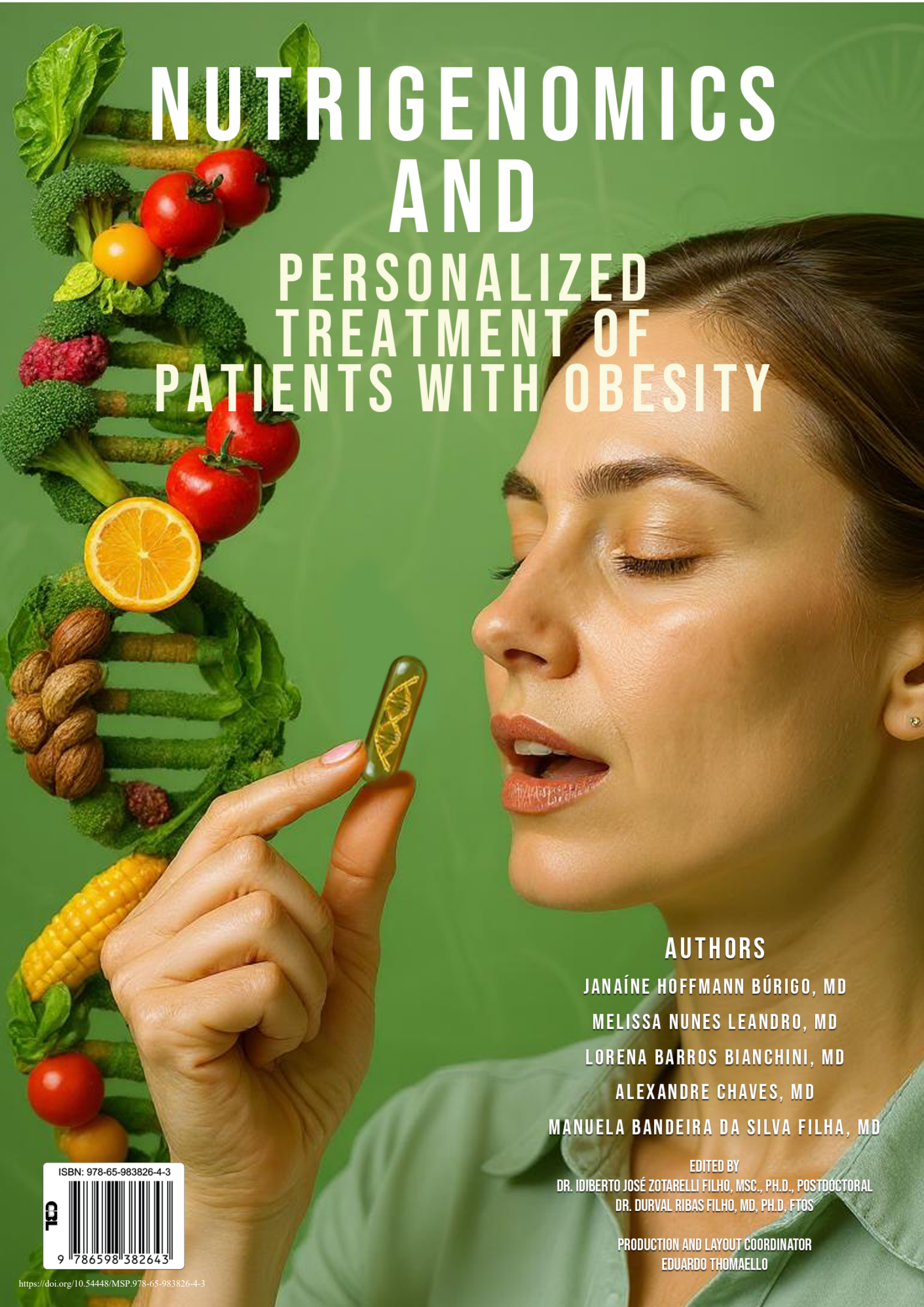
NUTRIGENOMICS AND PERSONALIZED TREATMENT OF PATIENTS WITH OBESITY



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Preface

Dear Reader

Obesity is a chronic, progressive disease, with multifactorial causes associated mainly with lifestyle (sedentary lifestyle, inadequate eating habits) and also with other conditions, such as genetic, hereditary, psychological, cultural, and ethnic factors. The World Health Organization (WHO) estimated that in 2016, there were approximately 1.9 billion (39%) individuals. In this scenario, nutrigenomics establishes personalized diets based on genotype, to promote health and reduce the risk of chronic non-communicable diseases such as obesity. Obesity is a disease characterized by excess adipose tissue, which may be of genetic origin, as seen in tumor necrosis factor (TNF), also considering environmental factors. Adipose tissue is also an endocrine organ with inflammatory functions, thus causing the prevalence of other diseases. The compounds present in food can modulate human genes, both positively and negatively, and are related to numerous pathologies. They are also considered modulators of the inflammatory response mainly due to their antioxidant action, thus helping obesity. Nutrigenetics understands the effects of genetic composition in response to diet, investigating the biological response to nutrients, while nutrigenomics is the science that studies the interaction between genes and nutrients, they propose to see individuals in a unique way differentiated by common genetic variations (polymorphisms) which makes the individual metabolically unique. Thus, genetic mapping may enable healthcare professionals to provide better assessments, enabling individual strategies for the treatment of various diseases. The doctor accurately evaluates the individual using, in addition to anthropometric parameters, knowledge of biochemistry and nutrition on an individual basis, evaluating the relationship between nutrients and genes. Thus, the present book aimed to present considerations and clinical approaches to the importance of nutrigenomics for the personalized treatment of patients with obesity.

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SUMMARY

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INTRODUCTION

Obesity is a chronic, progressive disease with multifactorial causes associated mainly with lifestyle (sedentary lifestyle, inadequate eating habits) and also with other conditions, such as genetic, hereditary, psychological, cultural, and ethnic factors [1,2]. Treatment is complex, long-term, and involves lifestyle changes, with an emphasis on nutritional therapy, physical activity, psychological interventions, and drug or surgical treatment [3-5].

As it is a chronic disease, the diet recommended for the treatment of obesity should contribute to maintaining the individual's overall health. The World Health Organization (WHO) estimated that, in 2016, there were approximately 1.9 billion (39%) individuals who were overweight (Body Mass Index - BMI > 25 kg/m2), of which 650 million (13%) were obese (BMI > 30 kg/m2). The global prevalence of obesity has increased substantially over the last 40 years [3]. In this context, with the completion of the Human Genome Project (HGP), whose objective was to sequence all of our genetic material, many studies have been carried out to elucidate the functions of genes and their interactions with the environment [5,6]. Genes can be defined as fundamental units of heredity that contain information for the production of different proteins necessary for the functioning of cells. According to the data obtained in the HGP, the human genome is estimated to be composed of approximately 30 thousand genes, which are responsible for producing more than 100 thousand different proteins [7,8]. The term genome refers to the set of genetic material found in the chromosomes of an organism. Humans normally have 23 pairs of chromosomes, of which 22 are autosomal and 1 is sexual (XX or XY) [9,10]. The HGP also allowed the identification of single nucleotide polymorphisms (SNPs), the main forms of genetic variation among individuals [7]. These polymorphisms may imply

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the production of proteins with altered functions, thus interfering with the balance between health and disease. SNPs can influence the individual response to diet [8]. Depending on the set of inherited SNPs, some people may become more susceptible to certain diseases, such as heart disease, cancer, and diabetes, among others. In the context of the post-genome era, different “omics” disciplines have emerged, with nutrigenomics standing out, which seeks to investigate the influences of nutrients and bioactive compounds in food on the way genes are expressed and how variations in the genome influence the way an individual responds to diet [7,8]. The concepts of nutrigenomics can be summarized as follows: diet acts on the human genome directly or indirectly, altering the structure and expression of genes; in certain circumstances, for some individuals, diet can be a serious risk factor for different diseases; some genes regulated by diet may play a role in the incidence, progression, and severity of chronic diseases; The degree to which diet influences the balance between health and disease may depend on genetic makeup; dietary intervention based on understanding nutritional needs and genotype can be used to prevent, inhibit, and mitigate disease [11-16]. Although human beings have distinct characteristics in terms of weight, height, skin color, and hair color, i.e., very varied phenotypes, their DNA is 99.9% similar. Thus, this small variation of 0.1% in the gene sequence plays an important role in differentiating one person from another and in susceptibility to disease. In this context, nutrients can trigger beneficial or unbeneficial molecular effects, and these actions depend on the individual genetic makeup and which genes have their activity altered [7-9].

In addition to polymorphisms, other factors, such as environmental factors, also influence gene expression, such as medications, pollutants, stress, and even diet. Considering that food represents the environmental factor to which we are constantly exposed, it is important to note that eating habits are the main factors responsible for

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changes in gene expression [7,8].

Future nutritional recommendations based on each person's genotype should be optimal for reducing the risk of these diseases and promoting health. In this context, different organizations have developed nutritional recommendations aimed at reducing the risk of diseases such as cardiovascular disease, cancer, and diabetes. However, it is important to note that not everyone would benefit equally from such recommendations since their establishment did not take into account the profound differences that individuals present in their response to diet. Thus, the objective of nutrigenomics is to establish personalized diets based on genotype, to promote health and reduce the risk of chronic non-communicable diseases [7,17-20].

Nutrigenomics can also be said to be an area of genetics that investigates how nutrients, through diet, can influence the gene expression of each individual. Studies in this area demonstrate that certain genes are capable of influencing the way the body processes certain nutrients, such as lipids and carbohydrates, and that different types of dietary patterns can affect the expression of these genes. A diet rich in saturated fats can affect the expression of genes related to the regulation of metabolism and, consequently, weight. This can lead to excess weight gain and obesity [21].

In this sense, nutrigenomics impacts obesity, which is a complex and multifactorial condition characterized by the excessive accumulation of body fat, and which can be influenced by numerous components, with the determining aspects being lack of physical activity, environmental determinants, inadequate diet, and genetic factors. And its reversal can be very well influenced by these last two associated elements [3].

Moreover, nutrigenomics should be seen as one of the aspects that can be used to prevent and reverse obesity, but not the only one. Other factors of great benefit are the

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adoption of a healthy lifestyle and the environment to which one is exposed which should be considered in the process of developing strategies to treat obesity at all stages, and even before its genesis [6,7].

Knowledge about nutrigenomics became consolidated from a large study started in 1990, called the Human Genome Project. This international research by scientists was concluded in 2003 when the complete sequencing of the human genome was considered to have been achieved [7]. Scientists managed to identify and map between 20,000 and 25,000 human genes. Some of the gains of the project were the discovery of new genes and genetic variants associated with human diseases, the understanding of the underlying mechanisms and complex diseases, and the identification of targets for the development of new nutritional and drug therapies [7,8].

By analyzing the human genome, scientists have been able to identify genetic variants that affect the metabolism of specific nutrients, which may help explain why some people are more susceptible to certain health conditions and diseases. It is important to emphasize that nutrition is a very broad and multifactorial area, which, in addition to the great influence of the human genome, both when moving towards and leaving a certain health condition, is influenced by environmental, behavioral, socioeconomic and socioemotional factors [21-23].

Therefore, this book presents the main considerations and clinical approaches to the importance of nutrigenomics for the personalized treatment of patients with obesity.

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CHAPTER I

Nutrigenomics and Obesity

After decoding the human genome and taking advantage of this valuable progress, nutritional sciences inaugurated an important exploratory milestone in the sense of understanding organic phenomena orchestrated by nutrients, but now based on variations within the genomic context [7]. To this end, they used molecular biology techniques and advanced the possibilities of interpretations of nutritional actions at the intracellular level, in an attempt to understand how certain cellular signaling pathways function or are controlled. In mid-2005, the term nutrigenomics gained strength, establishing a new branch of science2. However, nutritional genomics brings together three main areas: nutrigenomics, nutrigenetics, and nutritional epigenetics (or epigenomics) [7,24-26].

While nutrigenomics seeks to understand the intracellular signaling pathways mediated by nutrients, with direct outcomes in the modulation of the gene expression pattern, nutrigenetics considers the presence of mutations/polymorphisms when interpreting the different organic responses in different individuals, but under the consumption of the same diet or nutrient. Nutritional epigenetics investigates mechanisms that control the genomic response pattern that can be affected by factors external to the organism, in this case by nutrients and diets, and also investigates the heritability of these mechanisms, which will exert control over descendants [27-31].

Nutrigenomics is explored as a tool for the possible management of several diseases, especially obesity. Despite the great investigative enthusiasm for this area of science, very little success has been achieved in practical terms, given the enormous functional complexity of the human genome, mutations, and the breadth of the diversity

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of environmental influences. However, this area of knowledge is strongly projected to the treatment and, mainly, prevention of diseases, even though there is little scientific evidence [7,32-36].

It is difficult to define which gene sets are the main ones that influence obesity or the obesogenic process. There are broad research fronts, both for prevention and treatment of the disease. For each phase of the disease, a set of genes stands out. There seems to be no doubt that the set of inflammatory genes is the most important since it participates in and practically defines the onset of metabolic errors, in addition to also being a determining factor in the chronicity and worsening of obesity, along with its comorbidities [37-40]. Diets with excess calories, especially those rich in saturated fats, trigger a low-grade inflammatory process. Other important sets of genes are modified, such as those that coordinate the function of the endoplasmic reticulum, the autophagic, mitophagic, and apoptotic processes [31,41,42].

After the onset of the inflammatory process, the signaling pathways that coordinate the aforementioned phenomena intercommunicate within the cell, making it difficult to determine the most important gene set. Taking resveratrol as an example of a bioactive compound investigated in several clinical studies, it is a stilbene belonging to the polyphenol class, abundant in the skin of purple grapes and in their derivative products. Studies describe its ability to control intracellular signaling pathways involved in food intake, energy expenditure, among others [43].

Ligt et al. (2018) [22] conducted a randomized, placebo-controlled study in which they offered 150 mg/day for 30 days to 13 patients with obesity and DM2. Compared to the placebo, the resveratrol group showed an increase in the function of mitochondrial complex IV and an increase in the number of mitochondria in skeletal muscle. Although the study did not show weight loss or improvement in insulin resistance, there was a clear

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demonstration of the possibility of the bioactive compound acting in the modulation of an extremely specific metabolic process.

Arzola-Paniagua et al. (2016) [23] reported weight loss in obese patients treated for 6 months with resveratrol (100 mg), associated or not with orlistat (120 mg), in a double-blind, placebo-controlled study. Compared to the placebo group, treatment with orlistat, a pancreatic lipase inhibitor used in the treatment of obesity by partially reducing intestinal fat absorption, was only effective in reducing waist circumference, percentage of adipose mass, serum leptin, and triglycerides when associated with resveratrol. The study suggests that these outcomes are due to the modulation of nuclear receptors and transcription factors responsive to resveratrol. The difficulty in demonstrating more robust cellular phenomena mediated by bioactive compounds in humans is also due to the need for tissue collection, something extremely limiting in these studies.

Thus, using basic science studies capable of supporting hypotheses sought in humans, critical analysis of scientific works is crucial, with rationalization regarding the treatment time, animal/cell species used, and, mainly, whether the doses and methods of obtaining the substances are feasible. For example, Arzola-Paniagua et al. (2016) [23] and de Ligt et al. (2018) [22] used 100 and 150 mg/day respectively for an adult patient, which is equivalent to approximately 1.8 mg/kg of weight for an 80 kg individual (also considering that both studies involved obese individuals), Shabani et al. (2020) [24] used approximately 300 mg/kg of animal body weight, in a diet offered to mice. In this study, they found significant changes in physiological parameters (weight, blood glucose, etc.) and mainly in the expression of genes that control immune function, such as CD4, CD8, CD11b, CD45, F4/80 (genes that control the macrophage action spectrum) and consequently changes in inflammatory cytokine genes (IL1β, IL6, IL10, TNFα, MCP1, etc.).

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Under the conditions of this study, it is necessary to understand whether the biomolecular modifications achieved could also be achieved in humans. To correctly calculate the dose, based on the two studies presented, it would be necessary to consume 24g of resveratrol in its isolated form, making its implementation unfeasible, since several side effects have been described for humans at doses above 1g per day [25], such as an increase in the content of endothelial adhesion proteins (VCAM and ICAM), inflammatory proteins (PAI1), high oxidation of LDL [26] or inhibition of the hepatic microsomal detoxification complex (P450), by reducing the content of the proteins CYP3A4, CYP2C9 and CYP2D6 [27]. Therefore, the dose-response concept must also be fundamentally considered for substances derived from food.

The intracellular signaling networks coordinated by nutrients do not function identically for all individuals (individual response), or even in the same way in all tissues. It is not surprising that there are different responses between two or more tissues to the same nutrient and dose since pharmaceutical sciences have long considered the effects to be so-called tissue-specific. However, to explain the differences in the action of a substance observed in the same tissue but between different individuals, it was necessary to advance in the constitutional analyses of the genome. Thus, to understand the different responses in different individuals mediated by the same nutrient or diet, nutrigenetics aims to investigate the interactions associated with genetic variability between individuals of the same species [28].

In nature, genetic mutations are a fundamental part of the evolutionary process and occur spontaneously (mainly) with the fusion of gametes. Various types of changes impact the nucleotide sequence, with biological repercussions that are sometimes insignificant, but other times devastating. Diseases caused by changes in a single gene are rare and are defined as monogenic diseases, such as phenylketonuria, sickle cell

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anemia, and Duchenne syndrome, among others. Monogenic obesity is also rare, with the most consolidated findings being the mutation in the leptin gene [28] in its receptor [29], in the proopiomelanocortin neurotransmitter [30], with early manifestation (childhood) of the morbid obesity phenotype in all cases. However, there are also diseases associated with mutations in several genes, called polygenic diseases, and this group is common to chronic non-communicable diseases.

Despite the broad involvement of genes, the phenotypic outcome is generally less significant compared to monogenic disease and, sometimes, even without manifestation of the phenotype. If the genetic mutation is found in more than 1% of the population, it is called a polymorphism, otherwise, it remains a mutation. In the area of nutrition, the main polymorphisms studied are those that affect only a single nucleotide, from the English Single Nucleotide Polymorphism, or simply “SNP”. Modern genome-wide association studies (GWAS) demonstrate an increasingly broad framework of possibilities regarding genetic interactions, their modifications, and interactions with environmental factors in hundreds of thousands of individuals [31].

Back in 1962, James Neel [32] postulated the hypothesis that type 2 diabetes mellitus (T2DM), for example, could be the result of a set of modifications in different genes that would converge together in the outcome of the disease. The term “thrifty genotype”, coined from then on, was quickly transposed to the condition of obesity. Studies continually seek to identify polymorphisms that are associated with obesity to predict, in healthy individuals, the possibility of phenotypic manifestation.

For example, FTO (fat mass obesity) is one of the most studied genes related to the search for polymorphisms associated with weight gain. In 2007, Frayling et al. [33], when analyzing 38,759 participants from 13 cohorts, identified a variant in the FTO gene positively associated with high body mass index (BMI) in 16% of homozygous adults

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carrying the T>A risk allele (rs9939609).

In Brazil, this same allele is associated with high body mass in children up to 8 years of age [34]. Taking the example of the FTO gene, although the aforementioned variant (rs9939609) is the most common one associated with the risk of weight gain, thousands of other variations have been described for the FTO gene, with many still lacking descriptions of their clinical significance or relationship with diseases [35] and, at least, presenting an outcome with benign clinical significance (https://www.ncbi.nlm.nih.gov/snp – filter: “benign”). Therefore, caution is needed when interpreting the identified variation.

Despite the various evidence regarding the rs9939609 variant of the FTO gene, in the DPS study on the prevention of T2DM, Lappalainem et al. (2009) [36] investigated a Finnish cohort with 522 middle-aged and overweight patients and concluded that the fact that the individuals were carriers of this variant did not hinder weight loss when lifestyle changes were adopted (restrictive diets and physical activity). The meta-analysis coordinated by Kilpeläinen et al. (2011) [37], containing 218,166 adults and 19,268 children, shows a 27% reduction in the association between the risk allele (FTO) and the chance of obesity when subjected to physical exercise. Similarly, in one arm of the PREDIMED (Prevención con Dieta Mediterránea) study, Razquin et al. (2010) [38] noted that when individuals, whether or not carriers of the FTO gene alteration, received a three-year intervention with a Mediterranean diet, there was more effective protection against weight gain in carriers of the variant.

This finding is attributed to the possibility that the components of the Mediterranean diet (oleic acid, hydroxytyrosol, etc.) compensate for the FTO failure in energy expenditure. GWAS studies have already identified several other modifications associated with weight gain, not only FTO but also the genes HTR2C (serotonin receptor),

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SH2B1 (SH2 domain-containing protein 1B), PPARg (peroxisome proliferator-activated receptor-gamma), LEP (leptin), LEPR (leptin receptor), ADRB2 (adrenoreceptor b2), UCP1/2 (mitochondrial uncoupling protein 1/2), TCF7L2 (transcription factor 7-like2), FABP2 (fatty acid-binding protein-2), among others. Based on the breadth of variants identified, "genetic panels" emerged in an attempt to associate several polymorphic genes with the outcomes described in the literature. However, it must be clear that having a certain polymorphism does not mean that the phenotypic manifestation is mandatory, that is, an analysis can't be deterministic. A recent study [39], part of the "DIETFITS" (The Diet Intervention Examining the Factors Interacting with Treatment Success) study, pre-selected 609 individuals with polymorphisms in the PPARg (rs1801282), ADRB2 (rs1042714) or FABP2 (rs1799883) genes to evaluate the interaction of these gene variants with two types of diets aimed at weight loss. To this end, the individuals were randomized into two groups, receiving healthy diets, but with low amounts of fat or carbohydrates. After 12 months of intervention, none of the genotypes investigated showed any type of significant influence associated with weight change. Furthermore, there was no interaction between the genotype of the individuals and the type of diet offered. It is expected that the more polymorphisms associated with a disease or signaling pathways that converge to the same disease, the greater the chance of manifestation of the phenotype. However, it is important to note that, just as an individual may carry genetic modifications that are associated with diseases, he or she may also carry modifications that protect the same condition. Furthermore, even if the individual carries this risk allele, the disorder is unlikely to occur without the individual being exposed to the environmental characteristics that promote that disease [40].

Nutrigenomics can be used to guide the consumption of a personalized diet for individuals in general, to ensure individualized care, especially for patients at higher risk

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of obesity, based on their genetics. For example, if a given individual's genome shows that they have a certain genetic variation that makes them less capable of processing carbohydrates, a low-carb diet may be the best option to avoid weight gain and obesity [41-44].

Nutrigenomics can prevent and reverse cases of obesity using data provided by the patient's genetic material, increasing reliability and reducing treatment time, costs, and health complications. Nutrigenomics is a faster and, therefore, less expensive option for reducing the global obesity rate, since its study can prevent obesity from taking hold, in addition to reversing existing cases. It is a more assertive care pathway, given that the patient's confidence is greater when they know that their care is based on genetic information [45,46].

Furthermore, genetics is defined as how genes are learned and their functions in hereditary inheritance, how certain conditions or traits are passed on to the next generation [7]. Genetics encompasses the study of the effects of genes scientifically, which are elements of heredity and have the role of carrying commands to synthesize specific proteins, which include examples of hereditary or genetic pathologies, such as phenylketonuria and cystic fibrosis [47].

In 1989, at the initiative of the international public consortium led by the National Human Genome Research, subordinate to the National Institute of Health of the United States, the human genome project was officially started under the direction of James Watson. In 1992, he was replaced by Francis Collins, who suggested 15 years for completion of the project, which would be delivered in 2003 [48]. The genome project was created to enable resources on genetic variations that increase the risk of specific diseases, such as genetic mutations that are frequently reported in cancer cells [49].

In May 1998, a private company, Celera Genomics, was created by John Craig

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Venter, a scientist and entrepreneur in biotechnology, who saw a possibility of profit by patenting genome positions, thus promising to complete the human genome project in 2001, ahead of schedule for the public consortium. Finally, the two groups, led by Francis Collins and J. Craig Venter, declared a joint victory, with the project officially completed in April 2003 [50].

The genotype corresponds to all of an individual's genes, and it is extremely important to understand how they are affected by environmental factors, such as physical exercise, stress, drugs, smoking, and diet [51]. Genomics is a newer way of studying all of an individual's genes. It assesses the interactions of genes among themselves and with the environment, encompassing the scientific study of complex diseases, such as heart disease, obesity, cancer, and asthma, which are generally caused by one or more combinations of environmental and genetic factors, and are offering new alternatives for treatments and therapies for such diseases, as well as new forms of diagnosis [7].

One of the sciences heavily investigated by this study was nutrition through the establishment of nutritional genomics. In recent years, there has been a major change in the perception of nutrition, characterized by a focus on pathologies with metabolic clinical symptoms, such as type 2 diabetes, cardiovascular diseases, and obesity. Nutritional genomics especially encompasses nutrigenomics and nutrigenetics, which demonstrate how the environment, genes, and nutrients interact and how these affect the phenotype, encompassing the risks of diseases [52].

Bouchard and Ordovas (2012) [49] state that nutrigenetics refers to the role of DNA sequence alteration in nutrient responses, while nutrigenomics is the study of the role of nutrients in gene expression. This research is based on the suspicion that there are individual differences in the efficacy of response to exposures to a particular nutrient or combination of nutrients.

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Nutrigenetics examines the individual's response to their eating plan and, with these individualities, identifies unique biological markers and how the individual genetic composition influences the outcome of the diet [53]. Nutrigenetics is related to the interactions between eating habits and the genetic profile of each individual. Therefore, it is based on the analysis of individual responses to specific changes in the eating plan and also on assumptions that these differences and responses are linked to the presence or absence of unique biological markers. Genetic polymorphisms can often predict each individual's response to the diet [54-56].

Homologous chromosomes are virtually identical to each other, but the DNA sequence can vary in specific locations on the chromosomes. When a variation is present in a population at a frequency greater than 1%, it is called a polymorphism [54,58]. Polymorphisms are also responsible for the variation in the human species, and different phenotypes are consequences of different polymorphisms, such as the ABO system. Polymorphisms can also directly induce risk conditions for diseases [59,60].

Nutrigenetics provides the basis for specific nutritional recommendations based on the individual's genetic makeup and investigations of various environmental factors, which will likely require individual verification of all synapses or, as predicted by others, whole-genome sequencing [61]. The main goal of nutrigenetics is to investigate the consequences of DNA modifications, including single-nucleotide polymorphisms, copy number alterations, and inclusion polymorphisms, on biological responses to the consumption of micronutrients and macronutrients, energy, and dietary bioactive compounds. Single-nucleotide polymorphisms (SNPs) are the most common types of variations in the human genome, with approximately 90% of all variations involving the substitution of just one nucleotide at a given DNA position [62].

Nutrigenomics encompasses the study of the relationships between the genome

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and diet, understanding how nutrients react to the way genes are transcribed and translated, in addition to subsequent proteomic and metabolomic modifications, and also changes in the response to dietary factors based on individual genetic composition. Individual characteristics, such as social status, physiological state, physical activity, sex, age, and specific conditions, such as risk of disease and pregnancy, can clarify the dietary support that best meets specific needs. In other words, gene expression communication, and discovering which genes are induced or repressed in the face of a given nutrient and how variations in the genome will influence the way the individual responds to the diet. Thus, the diet reflects the relationship in gene expression, making it possible to understand how the nutritional composition of foods modifies gene expression [63-65].

Also, nutrigenomics aims to understand how food components relate to genes and their results in modifying the phenotype, which is a manifestation of characteristics in the organism resulting from the interaction between genes and the environment [66]. This science is extremely important for nutrition since based on knowledge of numerous genetic individualities, personalized and individualized dietary plans can likely be prescribed, thus providing quality of life [67,68].

Precision nutrition has a very promising future since it evaluates the genetic characteristics and phenotype of the individual, aiming at both the treatment and prevention of diseases such as obesity. Genetic test panels have emerged that identify genetic variance, called risk alleles, which may be a key to understanding metabolic diseases and their associated therapies. This genetic information, combined with anthropometric, biochemical, and dietary assessments, will considerably increase the ability of health professionals to recommend a personalized and individualized diet [69-71].

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CHAPTER II

Interaction of Eating Habits

Obesity is characterized by an increase in adipose tissue weight, which results from an imbalance in homeostasis and energy due to excessive food intake compared to basal energy expenditure, influencing glucose metabolism, immune response, vascular homeostasis, among others [72]. Authors state that obesity is a complex disease with multiple etiologies, with its own pathophysiology. For its treatment, it is essential to accept the problem as a disease.

In this context, the increase in the global prevalence of obesity is mainly attributed to negative changes in lifestyle, which affect a certain vulnerability or genetic predisposition to obesity. In these circumstances, the obesity phenotype, of which four types are distinguished according to the anatomical distribution of body fat, namely global, android, gynoid, and visceral, is also influenced by environmental factors and genetic bases. The change in the anatomical position of body fat is a relevant morphological indicator associated with metabolic and endocrine alterations [73-75].

In gynoid obesity, known as pear-shaped, fat accumulates in the buttocks, hips, and thighs and is characteristic of women. This type of obesity is associated with hormonal and circulatory problems. In android obesity, known as apple-shaped, fat accumulates mainly in the abdomen, predominantly in men. This type of obesity is related to numerous metabolic disorders, such as high blood pressure, lung problems such as sleep apnea, dyslipidemia, heart problems, glucose intolerance, etc. Visceral adipose tissue consists of fat stored inside or near the viscera of the abdominal cavity. Excess fat between the viscera increases the risk of stroke, among other pathologies associated with obesity [76].

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In addition to storing energy, adipose tissue is an endocrine organ that secretes various substances, such as adipokines, which can act as pro-inflammatory or anti-inflammatory [77]. Adipose tissue is not only a storage organ; it also produces certain bioactive substances such as interleukin 6, which have inflammatory functions. With the high production of adipose cells, there is a change in the production of inflammatory adipokines, and therefore, the greater the amount of adipose tissue, the greater the secretion of these adipokines, such as tumor necrosis factor TNF-α and interleukin 6. Interleukin 6 and TNF-α are adipokines with an immunological function and are produced by adipocytes in response to infectious or inflammatory stimuli [78,79].

Obesity is a highly heritable trait, but it is not known whether the specific underlying genetic variants predominantly influence food intake or energy expenditure [77]. Mutations in genes related to monogenic obesity that are the result of the mutation or deficiency of a single gene have been studied, such as the genes associated with leptin and its receptor. The predisposition to obesity describes the polygenic character in which several pairs of genes interact to determine a characteristic. Thus, the association with other genetic variables relates to the individual in different ways. Specific genetic variation influences the individual in different ways, thus it is noted that the influence of diet can modify the state of health and disease through the relationship between nutrients and genes [80].

Authors expose different individualities in the capacity to respond to acute or repeated exposures to a certain nutrient or combination of nutrients. Throughout human history, diet has affected gene expression, resulting in phenotypes capable of responding successfully to environmental challenges and allowing better exploitation of food resources. These adaptations were fundamental for human growth and development [81-83].

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Changes in the nucleotide sequence of a gene are considered mutations. They frequently occur due to intracellular episodes, both as the action of free radicals reached in cellular processes, and as consequences of environmental events, such as ultraviolet rays. Mutations can be both harmful and beneficial, contributing to a positive change, or causing defects that compromise the individual's life [84-86].

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CHAPTER III

Genetic Polymorphisms

Conti et al., (2010) [60] explain that single nucleotide polymorphisms exist in the millions in the human genome. Synapses can often lead to changes in the structure, function, quantity, or location of encoded proteins, altering numerous physiological processes. In addition to interfering with physical characteristics, synapses can also influence the risk of chronic non-communicable diseases, nutrient requirements, and response to food. It is important to emphasize the importance of understanding that peculiar phenotypes result from the interaction between genes and the environment since a given gene can express different phenotypes depending on what it is exposed to [87].

For Rocha et al., (2007) [87], polymorphisms can act as genetic markers, since they are transmitted and related to other genes located in the chromosomal region close to them. Frayling et al. (2007) [69] when researching a possible action of the fat mass and obesity-associated (FTO) gene, which in Portuguese means associated with fat mass and obesity, in the development of type II diabetes, found that for people with two copies of the A allele, a 1.3 times greater chance of manifesting the disease. However, after statistical adjustment for body mass index, the association between type II diabetes and FTO was eliminated, suggesting that it was mediated by the occurrence of overweight or obesity.

Since then, studies have been directed to investigate the relationship of the FTO gene with excessive fat accumulation and its interaction with behavioral factors. The FTO gene has shown strong variations related to obesity. There is a subpopulation with severe obesity that manifests binge eating disorder. Due to its manifestation in the hypothalamus,

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FTO may be related to the expression of satiety, as a consequence, it exerts a function of the disorder contributing to obesity and its consequences [69].

Frayling et al., (2007) [69], researched a sample of 38,759 European volunteers and found a frequency of 16% of homozygous individuals. A for the single nucleotide polymorphisms rs9939609 of the FTO gene. This allelic group entered the logistic regression model with a probability, approximately, 1.2 times greater of being overweight, with a body mass index (BMI) greater than or equal to 25 kg/m^2 or 1.3 times greater than being obese, with a BMI above 30 kg/m^2.

Although BMI was the only variable that entered the regression model, on average, those classified as obese had a larger waist circumference and greater skin fold thickness, which demonstrates a greater amount of body fat in these individuals. In a study carried out with 2,900 people among children and adults from Europe [53], homozygous A for the SNP rs9939609, of the FTO gene, presented a 22% chance of having severe obesity. Both sexes of adults who carry the TT allele (homozygous T) for rs9939609 are 3 kg lighter on average compared to homozygous A (DINA et al., 2007). This indicates that homozygous T has a lower body mass index. For each transcript of the A allele that a person has, there is normally an increase of 0.4 kg/m^2 in BMI.

Lima et. al., (2009) [78] state that other researchers have found an association between the presence of the AA alleles and the manifestation of a greater amount of relative body fat. Different results were found in populations of oceanic islands such as Malaysia, Micronesia and Polynesia. The FTO gene and its relationship with BMI were investigated. 73% of the 320 volunteers were obese with BMI greater than or equal to 30 kg/m^2. No association was found between FTO polymorphisms and the presence of obesity.

For Lima et al., (2009) [78] the authors suggest that perhaps another

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polymorphism of the FTO gene is more active in this population because no association with the FTO gene was found in this population. Furthermore, people who are associated with this gene tend to have a greater predisposition to fatty foods and hyperphagia, having a greater chance of regaining the weight lost after weight loss. Knowing the modifications of the FTO gene can prevent weight regain and help with weight maintenance, thus guiding the nutritionist to obtain exact strategies that contribute to the treatment of obesity.

Molecular studies have shown that genetic polymorphisms may be associated with overweight and obesity [88-93]. Sippel et al., (2014) [94], describe leptin as a hormone secreted by subcutaneous adipose tissue in response to fat storage or excess food intake and is an important marker of the amount of adipose tissue. Leptin reduces appetite by inhibiting the formation of appetite-related neuropeptides and by promoting increased expression of anorectic neuropeptides. Congenital deficiency of this hormone is responsible for 1 to 2% of cases of early morbid obesity [68].

Campos (2015) [55] determined that deficiencies of micronutrients such as vitamins K and A are constantly reported in obese individuals. These micronutrients can directly affect the modulation of gene expression in adipose tissue cells and, as a consequence, the biology of the tissue. These nutrients can help reduce obesity and related pathologies, due to their ability to regulate gene expression and modulate adipogenesis and the inflammatory process.

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CHAPTER IV

Genetic Polymorphisms and Obesity

Some compounds present in food identified as modulators of the inflammatory response can help the process of disinflammation. Bastos et al., (2009) [47], describe the common antioxidant action of these compounds since they modulate the expression of genes that encode proteins involved in intracellular defense mechanisms against degenerative oxidative processes of cellular structures, such as DNA and membranes. The same authors also report that bioactive compounds (BACs) can activate, for example, adaptive intracellular signaling pathways against oxidative stress and exposure to the environment. Bioactive compounds exert health benefits, at least in part, by acting as "low-dose stress agents" or pro-oxidants and preparing cells to resist the most severe stress conditions: low doses activate signaling pathways that result in increased expression of genes, which encode proteins aimed at cellular protection.

Insufficient intake of these bioactive compounds from plants is essential to achieve the full, genetically determined load of quality of life and longevity [95,96]. Thus, according to this paradigm, chronic diseases such as obesity are also associated with deficiencies of substrates with functional properties. Polyphenols modulate several signaling processes in cells, such as cellular characteristics, inflammatory genes in macrophages, differentiation, and host. Recent studies suggest that they can modify the functionalities of signal translation pathways to promote benefits [85].

The anti-inflammatory action, referred to as the presence of phenolic groups in its molecule, occurs by interfering with inflammation pathways [84]. Resveratrol, which is a natural polyphenolic compound available especially in grape skins, is well known for its phytoestrogenic and antioxidant properties [52]. Bastos et al. [47] reported that this

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compound inhibits in vitro the expression of pro-inflammatory cytokines in lung cells stimulated by lipopolysaccharides and suppresses the activation of nuclear transcription factors kappa B and activator protein-1. The anti-inflammatory effect related to resveratrol probably results from its related action on the NF-kB signaling pathway [41].

For Fremont et al. (2000) [70], it was shown to modulate lipid metabolism and inhibit the oxidation of low-density lipoproteins and platelet aggregation. In addition, the phytoestrogen present in resveratrol may provide cardiovascular protection. This compound also has anticancer properties. A study conducted in male mice with resveratrol was evaluated in a cohort of C57BI\6J line mice that received a dose of 200 or 400 mg/kg/day (mpk) of resveratrol dominated by a high-fat diet with the same caloric value for both groups for 15 weeks. There was a significant decrease in fat that was also reflected in the white fat blocks, increased mitochondrial activity, greater aerobic muscle capacity, muscular resistance, and improved insulin sensitivity in a diet-induced obesity model.

Indian saffron, with the botanical name *Curcuma longa L.*, belongs to the Zingiberaceae family of Asian origin. It is a species known for its medicinal potential, as it contains the active ingredient curcumin and is also known as a spice plant, it is herbaceous and perennial. Due to these characteristics, there may be confusion with the species *Crocus sativus L*., commonly known as true saffron [66]. The literature describes the anti-inflammatory function of curcumin, due to its antibacterial, antiviral, antifungal, antitumor, etc. action [91]. Curcumin acts on several pathways of expression of proinflammatory cytokines, such as interleukins (IL-1, IL-2, IL-6, IL-8, IL12), tumor necrosis factor (TNF-α), and chemokines. In low doses, it also acts on antibody responses.

Bastos et al. (2009) [47] thus suggest that its anti-inflammatory effect is due in part to its ability to “sequester” reactive oxygen species in situations of cellular oxidative

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stress. This compound has shown several pharmacological activities in chronic health problems, such as arthritis, type II diabetes, atherosclerosis, multiple sclerosis, and Alzheimer's disease. In addition to hindering the replication of the human immunodeficiency virus (HIV), helping with wound healing, preventing liver damage, cataract formation, and its activity in fighting cancer are being widely investigated, having great importance in the prevention and treatment of various types [73].

Evidence suggests that curcumin may regulate lipid metabolism and play an important role in obesity. In a study conducted with adult C57BL\6 mice, it was possible to conclude that turmeric intake probably prevented 34.6% of the groups of animals that consumed a balanced diet supplemented with turmeric, since they had a significantly higher food intake and gained less weight, in addition to having increased brown tissue in the same group. However, further studies are needed to confirm such benefits [93]. However, the clinical application of curcumin is hampered by its low solubility in water, rapid metabolism, and low availability after oral administration [91].

Scholze (2014) [91] also reports that to improve the bioavailability of curcumin, several studies have been analyzed. Some of these approaches involve the use of adjuvant additives, such as piperine, a component extracted from black pepper seeds, promoting a higher plasma concentration of curcumin. Another active adjuvant is quercetin, a flavonoid that increases bioavailability in the intestinal mucosa when ingested with curcumin. The use of phospholipid complexes improves gastrointestinal absorption by decreasing elimination, thus increasing plasma levels of the compound [96-99].

The use of nanoparticles can also improve bioavailability due to solubility and biodegradability in the solid state, thus creating strategies for turmeric to be encapsulated in these materials [100]. Several studies have shown the benefits of green tea, obtained through the fresh leaves of the Camellia Sinensis herb. Green tea contains a significant

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amount of flavonoids known as catechins, promoting a decrease in body fat, and aiding in the treatment and prevention of obesity and related diseases such as dyslipidemia, diabetes, and cardiovascular disease [67].

Numerous classes of phenolic chemical compounds or flavonoids are included in green tea, in addition to caffeine, amino acids, carbohydrates, minerals such as calcium, iron, zinc, potassium, magnesium, and micronutrients such as vitamins B, E, and C [101]. The use of catechins present in Camellia Sinensis plants plays a valuable role in the control of adipose tissue due to their thermogenic action, which can increase energy expenditure in 24 hours and lipid oxidation, contributing to weight loss [92].

The high levels of flavonoids in green tea can protect tissues from oxidative damage and cells, eliminating free radicals. Tea flavonoids can thus be activated as antioxidants in the digestive tract and also in other tissues after absorption [86]. Due to their reported antioxidant action, flavonoids help in the oxidation of low-density lipoprotein LDL cholesterol, which causes the formation of atheromatous plaques [79]. The benefits of green tea have also been associated with maintaining and increasing bone mineral density, reducing the risk of hip fractures. Each individual has their own characteristics and dietary needs, and it is up to the nutritionist to adapt individual recommendations with the information contained in the genome, which will be essential for nutritional diagnosis and thus preventing obesity [60].

Recent advances in genomic technologies have made the acquisition of personalized genetic information easily obtainable. Direct-to-Consumer (DTC) personal genetic tests aim to provide consumers with information about their genetic ancestry, ability to metabolize nutrients and medications, and risk of developing diseases. One class of genetic tests offers personalized DNA-based dietary advice to improve health [102]. Nutrigenomics (or nutritional genomics) is the study of the relationship between genes

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and diet and is used as an umbrella term for two complementary approaches: how nutrients affect genetic function and how nutrients affect genetic function [103].

Variation affects nutrient response. The latter is sometimes referred to as nutrigenetics and includes the study of how genetic variations affect food intake and eating behaviors. The DTC marketing method facilitates the sale of genetic tests without the involvement of a healthcare professional. These tests are commercially available via the Internet and are largely unregulated, although significant steps are being taken to regulate this emerging market in certain jurisdictions [102,103].

The cost of the different types of genetic tests available can range from approximately US$99 to over USD 2,000. DTC genetic testing for disease susceptibility remains controversial, with opponents arguing that the tests have limited value due to questionable clinical validity and utility. Critics note that predicted risks will continue to change as new genetic variants are discovered, and therefore any risk estimates for diseases based on currently known common variants are premature [102,103].

Furthermore, environmental factors such as diet, smoking, and physical activity can have a much greater impact on risk but are often not considered when providing risk estimates. There is also concern that consumers may experience anxiety if they are given higher risk estimates for developing certain diseases based on their genes and may seek potentially unnecessary health interventions [102].

Another criticism of most DTC genetic testing is that the corresponding counseling is not genuinely personalized, since lifestyle recommendations are generally the same regardless of genotype. Despite these criticisms, proponents of DTC genetic testing argue that there is a public interest in genomics and that individuals should have access to their genetic information. Furthermore, some propose that direct access to genetic information may motivate consumers to adopt lifestyle and behavioral changes

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aimed at reducing the risk of disease development [104].

Studies have reported mixed findings on the effects of disclosing genetic risk information on health-related behaviors; However, only one study has investigated the impact of DTC genetic testing on behavior, and it did not report short-term changes in specific eating or exercise behaviors. A limitation of this study is that the genetic risk scores that were given to subjects were not specifically linked to a particular lifestyle behavior, and no personalized advice was given to reduce the risk of developing a health problem. Importantly, there was no control group in the study [105].

A recent survey of Nature readers shows that 27% of respondents who had their genomes analyzed changed their diet, lifestyle, or medication based on their genetic information, suggesting that genetic information could impact behavior. For appropriate recommendations and regulations regarding DTC genetic testing to be made, public knowledge and opinions about these technologies need to be well understood. Several studies have examined awareness of and attitudes toward DTC genetic testing among the general public or healthcare providers [103].

These studies report low awareness of genetic testing among the general public (13–24%), but higher awareness among healthcare providers (42-44%). Studies have reported interest in genetic testing among the public, with 50-66% of individuals reporting a willingness to undergo testing. Focus group surveys have also been conducted to better understand consumer and healthcare provider knowledge and attitudes toward nutrigenomics [106–108].

The majority of consumers in the focus groups were unfamiliar with the term nutrigenomics and did not relate the term personalized nutrition to an individual’s genetic profile, whereas about half of the health care professionals were familiar with the term nutrigenomics. After receiving an explanation of nutrigenomics, consumers felt that a

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personalized diet could help reduce the risk of developing diseases, whereas healthcare professionals expressed more skepticism [108].

Although these studies provide valuable insights into public perceptions of nutrigenomics and genetic testing, they were all observational or qualitative in design. Furthermore, there has been some concern that the genetic information obtained from a DTC genetic test is not always understood, and no studies have examined whether DTC genetic tests that provide personalized nutritional advice are understandable [107,108].

The growing obesity epidemic has coincided with a profound change in our living environment, such as unhealthy dietary patterns, sedentary lifestyles, physical inactivity, and poor sleep habits, as well as changes in demographic and cultural context [109]. In a recent US national cohort study, the magnitude of the association between obesity, as assessed by body mass index (BMI), and genetic risk of obesity was stronger in more recent birth cohorts than in earlier birth cohort years, suggesting that such a genetic predisposition to obesity may have a greater effect in more recent obesogenic environments [110].

Although environmental risk factors are largely modifiable and the development of obesity is essentially preventable, genetic variants associated with adiposity may also influence behavioral responses, such as appetite formation, total energy intake, and macronutrient preferences [111-114]. Furthermore, food preference patterns (such as high sugar and carbohydrate consumption) [115,116] would be partly genetically determined.

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CHAPTER V

Major Clinical Findings

The genetic contribution to obesity has been extensively investigated in genome-wide association studies (GWAS) [117–119], which have successfully discovered susceptibility loci and revealed mechanisms. However, predicting disease risk from the genetic context is complicated by interactions between genetic variants and environmental risk factors. Gene-environment interactions are ubiquitous and may account for the majority of disease risk observed across genotypes [120]. With rapid advances in omics technologies and analytical approaches, recent genome-wide analyses have revealed the genetics of intermediate phenotypes, such as circulating metabolites (metabolomics) and gut microbiome [121-126].

Integrating information from metabolomics and gut microbiome studies will provide new insights into the roles of gene-environment interactions in complex traits, including obesity, and will contribute to the precise prevention and management of obesity. Here, we highlight data from recent studies on gene-diet interactions in obesity and discuss how these findings can inform understanding of a more complex architecture of interactions between genes and environmental factors in obesity and associated diseases [127].

The genetic basis of complex metabolic diseases such as obesity and type 2 diabetes has increasingly been revealed [128,129], however, the genetic variants identified to date explain only a small proportion of the heritability of the diseases, suggesting so-called ‘missing’ heritability [130]. For example, the recent GWAS from the Genetic Investigation of Anthropometric Traits (GIANT) consortium identified a total

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of 97 loci associated with BMI; however, these loci account for only 2.7% of the BMI variation [119].

As others have previously described [131-134], the importance of studying gene-environment interactions has been well recognized, and the lack of heritability of obesity may be partly due to interactions between genetic variants and environmental factors such as lifestyle and dietary factors. Genes may trigger disease occurrence when a person with a high-risk genetic profile is exposed to high-risk environmental factors in the phenomenon of gene-environment interactions [135]. Gene-environment interactions may reflect a causal mechanism in which both environmental variants and exposures contribute to the causation of a disease or condition in the same individual, with genetic factors influencing sensitivity to environmental factors.

How these two exposures synergistically affect disease vulnerability remains to be resolved. In particular, obese individuals are characterized by different body shapes, and considerable heterogeneity may exist within the spectrum of clinical obesity [136-145]. A recent GWAS identified genetic variants associated with overall body shape based on a combination of multiple anthropometric traits [146]. To support gene-diet interactions and precision nutrition in obesity, it would be necessary to consider different body shapes and obesity subtypes.

Epidemiological studies have consistently demonstrated that specific diets and lifestyles increase obesity risk among genetically high-risk adults. For example, replicable evidence has shown that sugar-sweetened beverages [147-149], fried food consumption [150], physical activity, and sedentary lifestyles interact with genetic variants in association with obesity [151-153].

Intake of free sugars or sugar-sweetened beverages is a determinant of body weight [154,155]. Previously, we reported significant interactions between genetic factors

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linked to obesity (assessed by the genetic risk score (GRS) based on 32 BMI-associated loci) and sugar-sweetened beverage intake in two US cohorts from the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study (HPFS). The genetic association with obesity was stronger among individuals with higher consumption of sugar-sweetened beverages compared with those with lower consumption [147].

In a recent study of Swedish adults, similar results were observed, and the association of sugar-sweetened beverages with BMI was stronger in individuals genetically predisposed to obesity [148]. Furthermore, another recent study reported similar interactions between a GRS for obesity and soft drink consumption to changes in BMI [149]. In a Hispanic population living in Costa Rica, there were significant interactions between sugar-sweetened beverage intake and the chromosome 9p21 variant in myocardial infarction, and high sugar-sweetened beverage consumption strengthened the genetic risk [156]. Sugar-sweetened beverage consumption has been implicated in driving the obesity epidemic [157]; recent reproducible evidence from these studies in US and European populations suggests potential interactions in the relationship.

A higher intake of fried foods, which increases energy intake, is considered one of the unhealthy dietary factors influencing the risks of overall and central obesity [158]. It was previously reported for the first time that fried food consumption interacted with genetic background to obesity in the NHS and HPFS cohorts, highlighting the importance of reducing fried food consumption among individuals genetically predisposed to obesity. The FTO genotype showed the strongest interaction among all obesity-predisposing variants [159].

In addition to fried foods, among participants in the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) population and the Multi-Ethnic Study of Atherosclerosis (MESA), higher saturated fatty acid intake was associated with higher

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BMI among individuals at genetically high risk of obesity [152]. In a study of three US cohorts, the association of the APOA2 −265T>C polymorphism and BMI was modified by saturated fat intake [153]. The results of the UK Biobank study [151] showed no significant interactions between BMI-GRS and consumption of fried foods or carbonated beverages. The analysis and definitions of soft drink consumption (as no data on type were available) and fried food intake (which was indicated by the combination of reported intake of fried chicken and French fries) were different from other studies, and habitual intake of these foods also differed between the populations studied [147-150].

A recent study including data from 18 cohorts of European ancestry investigated whether a composite score representing a healthy diet (which was calculated based on self-reported intake of whole grains, fish, fruit, vegetables, nuts/seeds and red/processed meats, sweets, sugary drinks, and French fries) modified associations of genetic variants associated with obesity using GRSs based on 32 single nucleotide polymorphisms (SNPs) associated with waist-to-hip ratio (WHR) of 32 BMI. Their results suggested that associations between genetic predisposition and obesity traits were stronger among individuals with healthier dietary scores [160].

Several studies have investigated a gene-physical activity interaction in obesity [161,162]. A meta-analysis showed that physical activity attenuated the influence of FTO variants on obesity in adults [161]. While greater leisure-time physical activity attenuated the genetic association, a sedentary lifestyle indicated by prolonged TV viewing was found to accentuate the genetic predisposition to high adiposity. It was shown that in both women and men from the NHS and HPFS cohorts, the genetic association with BMI was strengthened with increasing hours of TV viewing [151].

A recent study from the UK Biobank also provides similar results, and the effect of genetic risk of obesity on BMI was stronger for people watching at least four hours of

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TV per day compared with those watching three hours or less [153]. The UK Biobank study also reported that associations of genetic predisposition and adiposity measures (such as BMI and waist circumference) were modified by a variety of sleep characteristics, including sleep duration, chronotype, daytime napping, shift work, and night work. Their results showed that the association between genetic risk and adiposity was exacerbated by adverse sleep characteristics.

Childhood obesity is a strong risk factor for metabolic abnormalities in later adulthood [163,164]. In line with the evidence in adults, studies have shown that the FTO rs9939609 genotype was associated with childhood obesity [165-168] and have also suggested an association of the FTO variant with food intake and preference [167,169]. We previously reported the results of a pooled analysis of 16,094 boys and girls from 14 studies and found that the BMI-increasing allele of the FTO variant was associated with increased total energy intake, but not with protein, carbohydrate, or fat intake. Furthermore, there was a significant interaction between the FTO variant and dietary protein intake on BMI, showing that lower protein intake attenuated the association between the FTO variant and BMI, with no heterogeneity across studies [169]. One study suggests an interaction between the FTO SNP rs9939609 and socioeconomic status in childhood obesity [170], and some other studies have reported gene-environment interactions in childhood obesity [171,172]. In a population-based longitudinal study in Brazil, vitamin D status significantly modified the effects of FTO on weight change in children, suggesting that the FTO SNP rs9939609 may affect childhood weight gain, and the genotypic effects were more pronounced among children with insufficient vitamin D levels [172].

How genetic variants modify the effect of dietary intake on weight loss among overweight and obese individuals has been reported. In participants from the Preventing

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Overweight Using Novel Dietary Strategies (POUNDS Lost) study [173] and the Dietary Intervention Randomized Controlled Trial (DIRECT) [174], a series of analyses of gene-diet interactions in obesity and metabolic risk factors have been conducted [175-202]. There has been debate about which dietary intervention is most effective in reducing body weight. According to a meta-analysis that evaluated the efficacy of different popular diets in improving weight loss among overweight and obese individuals, significant weight loss was observed with either a low-carbohydrate or low-fat diet, and differences in weight loss between individual diets were small [203].

Findings have consistently shown that the effect of low-calorie dietary interventions varying macronutrient content differed by genetic background, including disease susceptibility, metabolic status, and food or nutrient preferences. Furthermore, considerable inter-individual variation in response to dietary interventions has long been observed, and genetic variations may at least partially account for such inter-individual variation. For example, low-fat dietary intervention was associated with greater weight loss among overweight and obese individuals with the IRS1 rs2943641 CC genotype [190]. Another study indicated that overweight and obese individuals carrying the T allele of PPM1K rs1440581 may benefit more in weight loss from a low-carbohydrate diet [194].

Moreover, individuals with obesity are at high risk of progression to type 2 diabetes, and previous GWAS have revealed susceptibility loci for type 2 diabetes [204-213]. It was examined associations between weight loss diets and a GRS for diabetes based on 31 diabetes-associated variants and assessed 2-year changes in markers of insulin resistance and β-cell function in the POUNDS Lost study. Lower GRS was found to be associated with greater decreases in fasting insulin, HbA1c, and insulin resistance as assessed by HOMA-IR, and lesser increases in insulin secretion as assessed by HOMA-

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B, particularly among participants consuming a low protein intake [179].

A significant interaction between GRS and dietary protein was found in these outcomes, and the genetic effect was the opposite among those consuming a high-protein diet. Furthermore, we have previously shown that changes in adiposity and metabolic response to weight loss diets varying macronutrient content were significantly influenced by several other individual genetic variants, such as those associated with obesity (FTO and NPY) and type 2 diabetes (TCF7L2 and IRS1, etc.). A genetic variant in the FGF21 region that determines the preference for carbohydrate intake was associated with improvement in obesity in the POUNDS Lost study [177].

Several studies evaluating gene-diet interactions support a concept of "precision dietary interventions" that take into account individual variability, determined by genome, metabolome, microbiome, and other compositions, in the design of interventions. Although more external replication is needed, accumulating data suggest that one dietary intervention may be more appropriate than others, based on individual variability. Personal information such as genotype is useful for predicting inter-individual differences in the effectiveness of dietary interventions; however, there are concerns about whether providing such personal information may induce adverse effects on individual behavior [211].

According to the results of a randomized controlled trial in healthy middle-aged adults [214], compared with standard lifestyle advice, providing additional personalized information about genetic risk (of type 2 diabetes) did not affect behaviors (such as physical activity and diet) among study participants. Furthermore, providing personal information about type 2 diabetes risk did not appear to cause anxiety in their study.

In addition to dietary interventions, bariatric surgery is also considered an effective treatment for patients with severe and complex obesity [215-217]. There is a

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significant genetic contribution to weight loss after Roux-en-Y gastric bypass (RYGB) surgery [218]. However, only a few GWAS have been previously performed to identify genetic variants associated with weight loss response after gastric bypass [219,220], and more work is needed to understand the role of genetics after bariatric surgery. Whether genetic variants can predict the efficacy of gastric bypass surgery needs to be examined further.

In addition, a growing number of research studies are revealing new genetic variants associated with diseases, and whether or to what extent modifiable factors would alter genetic risk needs to be further investigated in the future. In a recent meta-analysis of diet/lifestyle intervention trials, the effect of weight loss interventions did not differ according to the FTO risk allele [221]. On the other hand, according to the results of the Look AHEAD (Action for Health in Diabetes) trial, genetic risk of coronary artery disease significantly predicted cardiovascular morbidity and mortality over nearly 10 years, and lifestyle intervention did not alter the genetic association [222].

In addition to classical environmental exposures, circulating metabolites can be used to predict the risk of metabolic diseases [223-225], as well as to assess weight loss in response to dietary intervention [226]. Metabolomics is the systematic study of small molecules generated by the process of metabolism and has made remarkable progress in understanding the mechanisms underlying metabolic diseases and predicting risk. Among several metabolites, circulating amino acid concentrations, such as branched-chain and aromatic amino acids, have been consistently associated with metabolic abnormalities, such as type 2 diabetes and obesity-associated insulin resistance [227,228].

Besides, disorders of taurine metabolism are closely linked to obesity, insulin resistance, and diabetes, and we recently reported that the effects of genetic risk of diabetes (assessed by 31 diabetes-associated variants) on changes in fasting glucose,

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insulin, and insulin resistance were significantly modified by circulating taurine among overweight and obese participants in the POUNDS Lost study. It was noted that elevated taurine concentrations were associated with a greater reduction in insulin resistance among individuals with a higher genetic risk of diabetes than those with a lower genetic risk [201].

Recent GWAS have revealed loci associated with intermediate phenotypes and circulating metabolites, and these variants would be useful for investigating the effects of the genetic determinant of metabolites in obesity [229-231]. According to the Mendelian randomization principle, genetic variants may be a better marker than biomarkers in assessing causal inference and are less likely to be affected by confounding and reverse causality. The associations between a genetic variant that determines amino acid metabolites and obesity have previously been examined in the POUNDS Lost study. Significant interactions were identified between dietary fat and a genetic variant rs1440581 near the PPM1K gene region that was associated with the ratio of branched-chain amino acids to aromatic amino acids (the Fischer ratio) on weight loss and changes in insulin resistance. The biological mechanisms underlying the metabolite associations and outcomes were different between participants. Further studies are needed to examine metabolomic approaches to gene-diet interactions to gain insights into potential mechanisms [194].

The gut microbiota may be a potential factor for the treatment of obesity and related metabolic diseases [229,230], and one study also showed that obese individuals with lower bacterial richness had greater weight gain. The potential influences of dietary habits on the gut microbiota have also attracted interest [19,122,123]. Long-term dietary habits have been shown to influence the composition of the gut microbiota [231], suggesting the importance of a well-designed study to investigate the interaction of long-

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term dietary intake and gut microbiota in the onset of metabolic disease. Circulating levels of a microbial metabolite, trimethylamine N-oxide (TMAO), have been associated with an increased risk of cardiovascular disease and mortality [232,233], and its precursor, betaine, has also been associated with cardiovascular disease and type 2 diabetes [234,235].

Although experimental studies in animals suggest the causality of the gut microbiota in the development of metabolic diseases, prospective cohort studies among healthy individuals are needed to investigate how altered or changing gut microbiota and its genome (metagenome) are associated with the risk of complex diseases [236,237]. Several studies have identified host genetic variants associated with the gut microbiota, and one study showed an interaction between host genetics and diet in regulating microbiome composition. The study identified a genome-wide significant variant in the LCT region that determines the abundance of Bifidobacterium in the gut microbiome, and the variant was also differentially associated with dairy intake. In a study of the elderly Mediterranean population, an association between the LCT variant and obesity was significantly modified by dairy lactose and milk intake [238], suggesting that alterations in the gut microbiota through the LCT genotype may be involved in the differences in dietary caloric extraction and obesity risk. Further studies considering the gut microbiome, related genetic variants, and dietary habits would be needed.

A major challenge when examining gene-diet interactions is whether the observations are replicable in other populations. Previous publications on gene-diet interactions in obesity have presented results from different populations to demonstrate that the results are replicable in other cohorts. On the other hand, large-scale collaborative studies are also needed to provide a higher level of evidence and to perform more detailed analyses, including different types of dietary factors, phenotypes, and different GRSs of

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obesity. Within the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) consortium, the authors have pooled results from multiple cohorts and meta-analyzed results to examine gene-diet interactions [239,240]. Population-wide biobanks have been established in several countries, such as the United Kingdom and China. Research-based on the large sample size of biobanks with electronic health records, available data on habitual dietary intake (such as using food frequency questionnaires), and other health data will contribute significantly to the identification of gene-diet interactions on various health outcomes. In addition, it is important to provide robust evidence on gene-environment interactions from a large-scale collaborative study in participants of randomized controlled trials. Different dietary interventions were introduced in each study, and testing gene-diet interactions is also a challenge.

Other challenges include the imprecise assessment of environmental exposures, the difficulty in defining causal variants, and the construction of standardized statistical models to detect interactions in different patterns. One study introduced a negative control variable to control for residual confounders and also considered the effects of 'heteroscedasticity' since overweight and obese individuals have a greater variation in BMI than non-overweight individuals, and these differences in BMI may create false positive evidence of interaction [151].

The obesity epidemic during the last decades coincided with a profound change in unhealthy dietary patterns, sedentary lifestyles, and physical inactivity. Genetic predisposition to obesity may have interacted with this obesogenic environment in determining the obesity epidemic. Increasing evidence has shown the potential effects of gene-environment interactions on obesity. Data from dietary intervention trials suggest that changes in adiposity and metabolic response to low-calorie diets for weight loss can be significantly modified by genetic variants, especially those related to obesity, type 2

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diabetes, metabolism, and food preference [152].

Although additional external replications and large-scale analysis are needed to confirm these results, the positive results obtained so far tend to support precision dietary interventions, considering genetic predisposition to diseases, genetic variants determining food preference and metabolites, as well as phenotypes and metabolite intermediates [153,239,240]. The idea of precision nutrition and dietary intervention is considered as each dietary habit and advice is individually tailored to prevent chronic diseases based on the genomic context, habitual food and beverage consumption, nutrient intake (especially those that contribute to disease risks), and also the metabolomics, microbiome and other omics profiles of an individual. On the other hand, few studies investigate the potential roles of metabolomic mechanisms and the gut microbiome that may act at the interface of genetic variation and the environment, affecting obesity and health. Research that integrates data on genes, dietary habits, metabolites, and gut microbiome into human health research would be one of the most interesting areas of precision nutrition soon [239,240].

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FINAL CONSIDERATIONS

It was concluded that obesity is a disease characterized by excess adipose tissue, which may be of genetic origin, as seen in tumor necrosis factor, and also considering environmental factors. Adipose tissue is also an endocrine organ with inflammatory functions, thus causing the prevalence of other diseases. The compounds present in food can modulate human genes, both positively and negatively, and are related to numerous pathologies. They are also considered modulators of the inflammatory response, mainly due to their antioxidant action, thus helping with obesity. Nutrigenetics understands the effects of genetic composition in response to diet, investigating the biological response to nutrients, while nutrigenomics is the science that studies the interaction between genes and nutrients. They propose to see individuals in a unique way, differentiated by common genetic variations (polymorphisms), which makes the individual metabolically unique. Thus, genetic mapping may enable health professionals to make a better assessment, enabling individual strategies for the treatment of various diseases. The doctor can accurately assess the individual using, in addition to anthropometric parameters, knowledge of biochemistry and nutrition on an individual basis, evaluating the relationship between nutrients and genes.

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Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

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Application of Artificial Intelligence (AI)

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NUTRIGENOMICS AND PERSONALIZED TREATMENT OF PATIENTS WITH OBESITY

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