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Genetics, Nutrition, and Health: A New Frontier in Disease Prevention

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ABSTRACT

The field of nutrition research has traditionally focused on the effects of macronutrients and micronutrients on the body. However, it has become evident that individuals have unique genetic makeups that influence their response to food. Nutritional genomics, which includes nutrigenetics and nutrigenomics, explores the interaction between an individual's genetic makeup, diet, and health outcomes. Nutrigenetics studies the impact of genetic variation on an individual's response to dietary nutrients, while nutrigenomics investigates how dietary components affect gene regulation and expression. These disciplines seek to understand the impact of diet on the genome, transcriptome, proteome, and metabolome. It provides insights into the mechanisms underlying the effect of diet on gene expression. Nutrients can cause the modification of genetic expression through epigenetic changes, such as DNA methylation and histone modifications. The aim of nutrigenomics is to create personalized diets based on the unique metabolic profile of an individual, gut microbiome, and genetic makeup to prevent diseases and promote health. Nutrigenomics has the potential to revolutionize the field of nutrition by combining the practicality of personalized nutrition with knowledge of genetic factors underlying health and disease. Thus, nutrigenomics offers a promising approach to improving health outcomes (in terms of disease prevention) through personalized nutrition strategies based on an individual's genetic and metabolic characteristics.

KEY TEACHING POINTS

- Genetic differences among individuals affect the metabolism, gene regulation, and sensitivity of disease in response to diet therefore traditional nutrition research expands to integrate the influence of genetics on the dietary response of an individual.
- Nutritional genomics which includes the reciprocal and complementary field of nutrigenetics and nutrigenomics, studies the interactions between gene and dietary components.
- Nutrigenetics studies the genetic effect on the metabolism of nutrients while Nutrigenomics explores the impact of nutrients on genetic expression thus shaping personalized dietary requirements.
- A personalized dietary approach based on comprehensive genomic profiling (genomics, proteomics, metabolomics, transcriptomics) can help to promote health and prevent illness.

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1. Introduction

Nutrition research has conventionally centered around the study of macronutrients (lipids, proteins, carbohydrates), micronutrients (vitamins, minerals), their physiological requirements, and the consequences of their excess and deficiency. It has become increasingly apparent that not every individual will benefit from the same dietary regime owing to their different nutritional phenotypes (response to dietary factors based on their genetic makeup). Humans share almost 99.9% of a similar genome with only 0.1% differences. This minor difference leads to variations in the physical characteristics of individuals (hair, eye color, height, weight) as well as their response to the ingested food (1, 2). The discipline of 'Nutrigenomics' emphasizes on the impact of bioactive compounds on the expression of our genes, which may either enhance the genetic potential or suppress their activity. The outcome relies on the behavioral alteration in the gene and the genetic expression (2). For example, interaction between nutrients and genes occurs through the capacity of certain compounds to bind to transcription factors. This binding process can either augment or obstruct the ability of transcription factors to interact with the components that regulate the binding control of RNA polymerase. Prior research has already demonstrated that certain constituents like Vitamin A, D, and fatty acids possess the ability to directly trigger nuclear receptors and stimulate gene transcription. Meanwhile, compounds such as resveratrol present in wine and soy genistein may indirectly impact

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the molecular signaling pathways, like the factor kappa B. The involvement of these factors in activating and regulating key molecules is associated with a wide range of diseases, ranging from inflammation to cancer (3). Single-nucleotide polymorphisms (SNPs) are the main reason for this genetic variation, and it can often change the encoded protein. Studies have shown that certain genes and their variants can be regulated or are influenced by nutrients/food compounds from the diet and that these molecular variations may have beneficial effect on an individual's health (4). For example, Fatty acids (FAs) and their corresponding compounds such as acyl-CoA or eicosanoids possess the ability to interact with specialized nuclear receptor proteins. These receptors bind to specific control regions in our DNA, referred to as promoters, and can impact the transcription of genes. The receptor proteins in collaboration with fatty acids, function as the transcription factors. FAs including eicosanoids, can directly bind themselves to two types of Peroxisome proliferator-activated receptors (PPAR), PPARα and PPARγ. Certain unsaturated fatty acids, like oleic acids, linoleic acid, alpha-linolenic acid, and arachidonic acid, act as potent stimulators of these receptors. These polyunsaturated FAs can also affect the proliferation of white blood cells together with the cells' tendency to undergo programmed cell death (apoptosis) or necrosis, and may also have an impact on the expression of various genes involved in processes such as glycolysis and lipogenesis (5). Thus, the study of this interaction between the human genetic makeup (human genome), diet, and its health consequences is termed as 'nutritional genomics'. This field encompasses both nutrigenetics and nutrigenomics, which are often used interchangeably (6).

The term 'nutrigenetics' represents the effect of human genetic makeup on various dietary nutrients and their metabolism. Whereas 'nutrigenomics' identifies the effect of nutritional components on gene regulation and gene expression, thereby helping to determine the dietary requirements of an individual (7). The latter aims to clarify the influence of certain dietary components (such as bioactive compounds and non-nutritive substances) on gene expression, which may either enhance or suppress the potential of a particular gene (8). Moreover, it also helps to determine the relationship between diet and the risk of chronic health problems like diabetes, CVDs, cancer, and obesity (Figure 1). This review aims to discuss the concept of nutrigenetics/nutrigenomics and its function in contemporary health care, specifically with regard to non-communicable diseases. It will further help the researchers to develop an approach for the management of chronic diseases. Through comprehensive genomic profiling, including genomics, proteomics, metabolomics, and transcriptomics, researchers can gain a holistic understanding of the unique metabolism of an individual and develop tailored dietary plans to promote health, prevent illness, and mitigate potential health risks.

2. Emergence of nutrigenomics and nutrigenetics

Nutritional research has been conducted since 400 BC when Hippocrates proposed that the warm body temperature was intrinsic. The so-called "analytical Chemistry Period" started around 1700 A.D. when Lavoisier identified the mechanism by which food was broken down by the body to produce energy, H_2O, and CO_2 (9). Antonie Lavoisier reported significant findings on food metabolism and its relationship with energy production, including its relevance to breathing and oxidation, between the 18th and 20th centuries (Chemical and Analytical Era of Nutrition). Later, in the nineteenth century's "Biological Era," studies on metabolism and chemistry were conducted, assisting nutrition science in defining their role in the emergence and prevention of chronic diseases like cancer, CVDs, neurodegenerative, and bone metabolism disorders. This period also marks the initiation of the Human Genome Project (HGP) which was first launched in the year 1990 and finally completed in 2003 (8, 10). Following the HGP, discussions, and endeavors on the "Post-Genomic Era" started, where advancements in "omics" science study were made possible by the development of bioinformatics. This era includes scientific advancements in nutritional pathophysiology and metabolism along with the integration of three disciplines viz. biological, social, and environmental (4, 11). Consequently, after genomics, other omics sciences such as proteomics, metabolomics, and transcriptomics emerged as ground-breaking concepts (4, 12, 13). Initially, nutrigenomics only included research on the effect of nutrients and bioactive foods on the genetic expression of an individual. This definition has lately been expanded, and nutrigenomics now includes research on dietary components that act as genome protectors. Therefore, this emerging discipline aims to comprehend the effect of dietary elements on the genome, transcriptome, proteome, and metabolome (2, 14). The scientific literature from the twentieth century contained the conceptual background, particularly for nutrigenetics, even though the words nutrigenetics and nutrigenomics were used more frequently in the healthcare literature during the first decade of the twenty first century. A significant portion of the early work in classical genetics focused on the genetic determination of dietary needs within a range of organisms, from unicellular to multicellular. But it wasn't until 1975 that Richard Brennan coined the term 'nutrigenetics' which made its way into the medical literature, particularly in regard to treating hypoglycemia. Contrarily, the term "nutrigenomics" was introduced in the year 2000, and since then, the term has gained popularity. Nutrigenetics and nutrigenomics are currently well-established specializations within the healthcare sector (6).

3. Relationship between nutrigenomics and nutrigenetics

Nutrigenetics and nutrigenomics are terms that are often used interchangeably not only within public literature but also within the professional nutritional and health sciences. The field of classical genetics is the origin of nutrigenetics. The chief objective of nutrigenetics is to investigate the effect of genetic variation, particularly in the form of single-nucleotide polymorphisms (SNPs), on the individual's response to food intake, especially the influence of genetic variation on an individual's metabolic state (15). However,

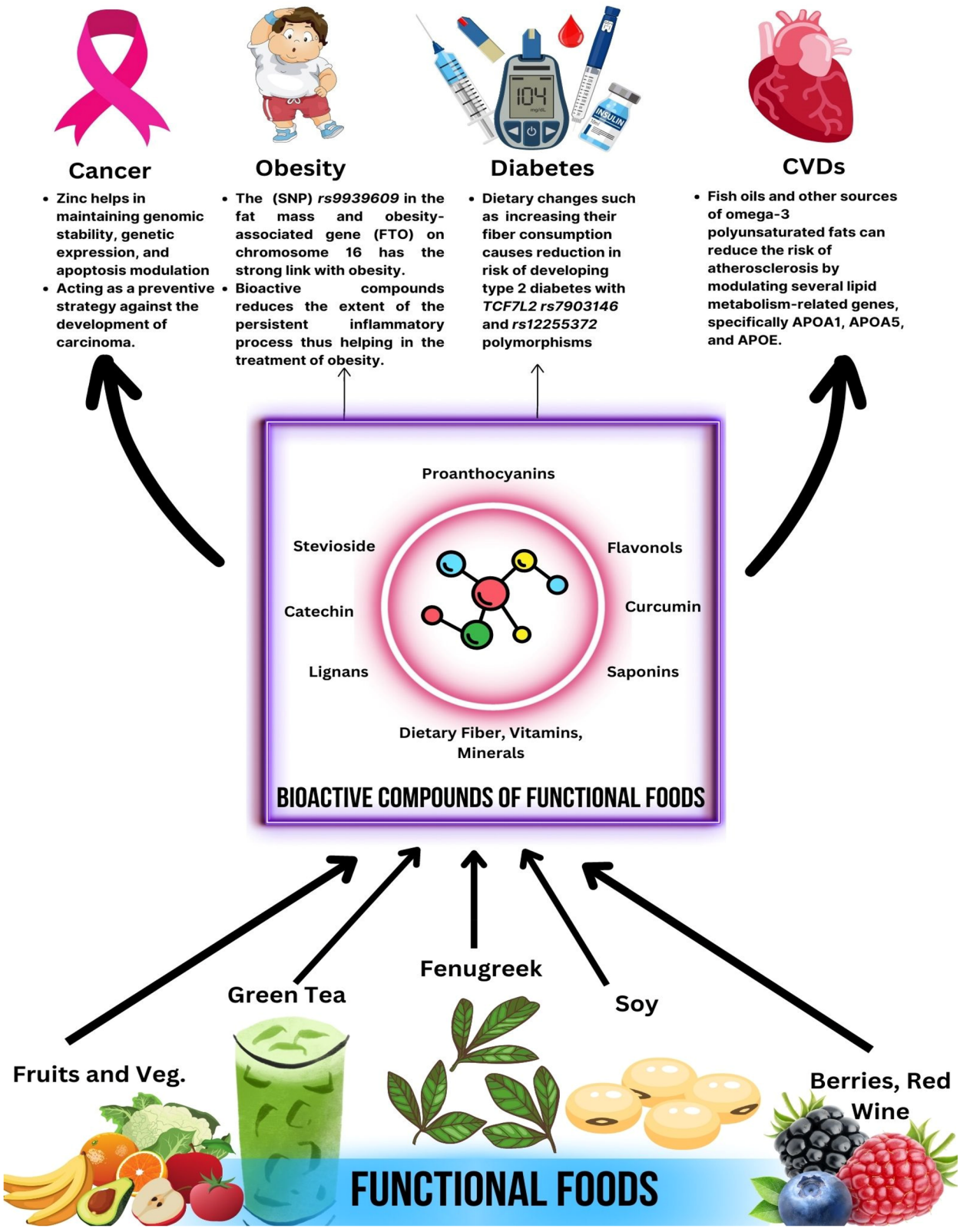

Figure 1. Bioactive compounds in functional foods and their role in lifestyle-related disorders.

'nutrigenomics' has its origin in the HGP, especially in the postgenomic era and its high-throughput omics technologies (16). Through epigenomic, transcriptomic, proteomic, and metabolomic high-throughput assays, it seeks to understand the manner in which food and nutrition affect gene expression (4). For example, the outcomes of metabolomic research conducted on premenopausal women indicate that soy isoflavone consumption significantly affects several metabolic pathways linked to osmolyte fluctuation and energy metabolism (17, 18). These biochemical alterations were amplified when miso or unconjugated soy isoflavone was consumed. Results from the study show that an individual's metabolism

is significantly impacted by the chemical makeup of *soycv3* found in the isoflavones. The long-term objective of nutrigenomics is to acquire and integrate a person's unique nutritional omics profile as well as the microbiome, which collectively makes up the 'gutome' (6).

Thus, the relationship between nutrigenetics and nutrigenomics can be described as reciprocal and complementary, which thereby addresses the question as to why the terms nutrigenetics and nutrigenomics are abbreviated as nutrigenetics/nutrigenomics. Based on this knowledge, researchers can design experimental studies in nutrigenomics using omics assays, from genomics to metabolomics to determine the precise mechanisms underlying the impact of diet on gene expression. Overall, the goal of nutrigenomics is to provide a complete picture of an individual's integrated metabolism to create a personalized diet to prevent illness and potential health risks, as well as to promote health and longevity (19).

4. Relationship between nutrition and gene expression

Personalized nutrition intake for optimal disease prevention is based on the genome of an individual because genetic variability may alter nutritional requirements and dietary intake among human sub-populations (20). The genetic profile affects the response of the body to bioactive food components by changing their absorption, metabolization, and target location (Figure 2). Nutrigenetics studies the impact of genetic variation, especially as a single-nucleotide polymorphism (SNP), on an individual's response to dietary intake. Both food preferences and the extent to which it is consumed are influenced by some specific genes. For example, *GLUT2* (glucose transporter type 2) genetic polymorphism is related to sugar-eating habits, suggesting a glucose-sensing mechanism that regulates food intake. Genetic variance in the *CYP1A2 gene* affects the sensitivity of a person to caffeine. This gene produces an enzyme in the liver that demethylates caffeine, and some gene variations demethylate caffeine more quickly than others (21). Another example is the glutathione peroxide gene polymorphism. Selenium supplementation has been linked to a reduced risk of lung, liver, prostate, and other cancers in human studies (20); however, the response may vary among two different individuals. Glutathione peroxidase is a selenium-dependent enzyme that functions as an antioxidant. Researchers have identified a polymorphism at codon 198 of the human Glutathione peroxidase gene, resulting in the substitution of proline with leucine amino acid. This genetic variation has been associated with an increased risk of lung cancer. Researchers have revealed that individuals with the (Pro/Lue) genotype had an 80% higher risk of lung cancer, while those with (Lue/Lue) genotypes had a 130% greater risk compared to those with the (Pro/Pro) genotype. The leucine-coding allele displayed a lesser susceptibility to increased enzymatic activity due to selenium supplementation compared to the proline-containing allele (22, 23).

Research studies also suggest the role of lycopene in lowering the risk of prostate cancer which is known to be impacted by *XRCC1 (Arg399Gln)* polymorphism (24). Genetic variations in catechol-O-methyltransferase, sulfotransferase, and UDP-glucuronosyltransferase affect the enzymatic function which is responsible for the metabolization of certain foods constituents (25). In women with the low-activity variant of catechol O-methyltransferase, green tea consumption was associated with a lower incidence of breast cancer. The methylation of catechins by this enzyme catalyzes their removal more rapidly from the body. Moreover, genetic polymorphisms can affect the digestion, absorption, and metabolization of certain dietary components (7).

The importance of nutrients comes from their potential to change transcriptional activation genes associated with various metabolic and clinical processes, including cancer and aging, by altering epigenetic changes like DNA methylation and histone modifications (26, 27).

Nutrients like folate, vitamin B12, methionine, choline, betaine, S-adenosylhomocysteine, and S-adenosylmethionine may have an impact on DNA as well as protein methylation. Epigallocatechin-3-gallate-rich green tea reduces DNA methyltransferase activity and triggers methylation-silenced genes in cancer cells (28). In addition to direct epigenetic changes, chromatin structure is frequently altered by various histone modifications, which appear to be equally essential in gene regulation and cancer (29). Bioactive constituents including curcumin, resveratrol, butyrate and sulforaphane have been reported to inhibit cancer cell progression by affecting the expression of specific apoptosis or cell cycle-mediating genes (30).

Another study conducted by Kussmann et al. (31) demonstrates that proteomics describes the response of the human genome to dietary changes, and it is a crucial component of nutrigenomics. Proteomics can be used to identify and measure bioactive proteins/peptides as well as it states the biological efficacy of food (31). Certain bioactive proteins are involved in colon cancer cell proliferation, differentiation, and apoptosis; the levels of which have been found to be altered after quercetin treatment. This proves the efficacy of flavonoids as anticancer agents (32).

Another effective method for determining the effect of diet on health is metabolomics. By looking for biomarkers derived from food, it is possible to determine inter-individual differences in the metabolization of identical foods in healthy and diseased states. The effectiveness of dietary intervention can be evaluated using metabolic patterns, food consumption biomarkers, and cohort studies to study diet-related disorders (33). In a research study, urine metabolites of premenopausal women who received soy in the form of miso (a source of unconjugated isoflavone and conjugated isoflavone glycosides) were evaluated. It was found that women who consumed soy had significantly more altered urinary metabolites indicating that isoflavone plays a major role in detecting any biological effects (17).

5. Applications of nutrigenomics

Researchers have been studying the effect of genes and gene variants on dietary requirements in recent years, leading to advances in the fields of nutrigenomics and nutrigenetics.

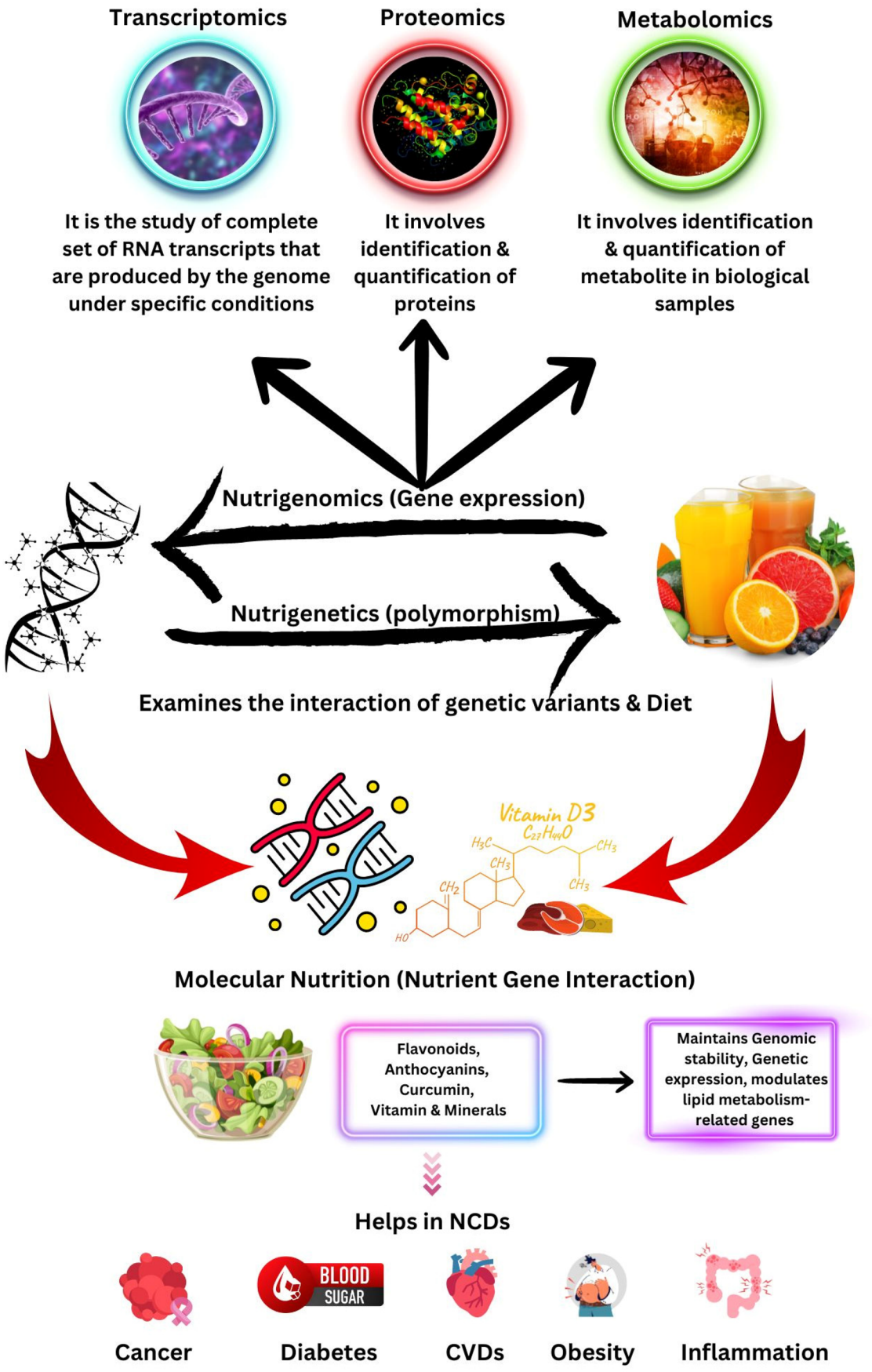

Figure 2. Nutrient-gene interaction and its role in disease prevention.

Using nutrigenetic approaches, it is now possible to combine the practical approach of personalized nutrition with knowledge of the genetic basis of health and disease. Nutritional experts are learning to analyze data on genetic variants, diet, lifestyle, and environment to create nutritional strategies based on genetic make-up, in the form of SNPs and lifestyle (34, 35).

5.1. Modern technologies used in nutrigenomics

Nutrigenomics is a multidisciplinary field that investigates the response of an individual to the interaction between genes and diet. This field explores the changes in genetic expression that lead to the transition of the body from a healthy state to a chronic illness which is governed by the chemicals found in the diet (36). It investigates the effects of diet and nutrition on gene expression using various high-throughput techniques such as epigenomic, transcriptomic, proteomic, and metabolomic analyses (3, 6). The wide range of variability in cancer prevention and risk can be attributed to the combined effects of nutrigenetics, transcriptomics, metabolomics, and proteomics (37).

5.1.1. Transcriptomics

Functional genomics methods serve as an effective strategy for the exploration of the genetic blueprint of an organism, which contains all the RNA transcripts such as mRNA, rRNA, tRNA, and other noncoding RNAs. This genetic information is stored within the DNA of the genome and is brought to life through the process of transcription. The non-protein coding RNAs hold diverse functions, while mRNA acts as a short-lived intermediary player within this complex network of information exchange. mRNA transcripts have gained recognition as reliable biomarkers for the identification of disease risk (2). Among the leading techniques in this field are microarrays that capture the whole genetic sequences, which focus on specific predetermined sequences, and RNA sequencing (38). Transcriptomics provides valuable insights into constituents of our diet. For example, a study involving transcriptomics delved into the molecular targets impacted by different food components. Work has been conducted by Davidson et al. (39) on approximately 9000 genes that were studied to determine the transformation within the colon cells of rat's DNA microarrays exposed to a carcinogen. The dietary variation solely varied around the type of fat consumed, comprehending n-6 polyunsaturated fatty acids (PUFAs), n-3 PUFAs sourced from fish oil, and n-9 monounsaturated fatty acids from olive oil. This exploration highlighted evident changes in the genetic makeup of the colonic epithelium, both during the initiation of malignancy and the promotional stage (7).

5.1.2. Proteomics

It involves a thorough study of peptides development and differentiation, particularly in relation to the progression of diseases through protein pathways that connect the external microenvironment to the activation of transcriptional processes (40). In the field of nutrigenomics, proteomics plays a crucial role by revealing the response of our genetic makeup to our dietary changes. Proteomics is being applied in the field of nutrition as it aids in identifying bioactive proteins and peptides, demonstrating the bio-efficacy of the diet (41). The field of nutritional science employs proteomics to uncover biomarkers that indicate fitness levels, diseases, potential treatments, and even predictions (7). For instance, the compound quercetin, found in flavonoids, exerts an influence on various proteins which is demonstrated by Wenzel et al. (32) who investigated quercetin-treated human colon cancer cells. The study revealed changes in many proteins, that are related to cell proliferation, differentiation, and apoptosis in colon cancer (41). The identification of these proteins as targets of quercetin may account for the anti-cancer properties of flavonoids. Moreover, researchers like Breikers et al. (42) explored the effects of increased vegetable consumption on the protein expression in the intestinal epithelium of healthy mice. It was found that approximately 30 proteins exhibited different expression levels due to enhanced vegetable intake. Among these, six proteins with varying activity levels could potentially contribute to the prevention of colorectal cancer. These findings support the idea that vegetables may play a role in reducing the risk of colorectal cancer (42).

5.1.3. Metabolomics

It refers to a group of molecules and compounds, collectively known as metabolites, which undergo many changes as a response to the evolving state of a cell, tissue, or organ (43). Metabolomics techniques are applied based on the shifts in the metabolism of glucose, to gain insights into the inner workings of bioactive food components and to understand different stages of carcinogen (7). Metabolomics emerges as a potent tool for unraveling the profound links between diet and individual well-being. Through the discovery of biomarkers derived from different foods, individual variations in the processing of nutrients by our body under normal and diseased conditions can be discovered. The potential of metabolomics extends to three crucial aspects of nutritional science: identifying biomarkers reflecting the intake of food, investigating disorders related to dietary habits, and the assessment of dietary intervention efficiency by evaluating intricate metabolic patterns (33). Collectively, metabolomics gives a deeper understanding of our body's interaction with the foods we consume, which can revolutionize nutritional assessment and healthcare practices.

5.2. Nutrigenomics and its relation to chronic diseases

Optimal nutrition plays a critical role in maintaining the homeostasis of an organism by providing energy as well as regulating the normal metabolism (3, 44). An individual's nutritional status is the result of the interaction of many variables, including genetic makeup, body composition, as well as emotional and social state. The nutrients and other bioactive compounds present in food may either prove to be beneficial for disease prevention (celiac disease,

phenylketonuria, diabetes, dyslipidemia) or may lead to nutrient malabsorption caused by certain anti-nutritional factors. Thus, nutrigenomics helps to better understand the relationship between genes and bioactive constituents obtained from dietary sources (45, 46).

The World Health Organization estimates that NCDs cause the deaths of over 40 million people annually. These chronic diseases include cardiovascular disorders, respiratory illnesses, obesity, diabetes mellitus, and cancer which are associated with faulty lifestyles such as consumption of alcohol or tobacco, physical inactivity, consumption of high-fat foods, etc. These illnesses pose a significant global burden on humanity, particularly for the developing world, both in terms of health and quality of life (4).

5.2.1. Inflammation

Inflammation results in response to any foreign substance viz. chemicals, microbes, and plant pollen that are recognized by the body which further triggers the immune response. Our body's adaptive immune system has a potent mechanism that aids in preventing infection and tissue repair. It may also be altered resulting in a wide range of chronic conditions. It is now well-established that controlling inflammation is a crucial strategy in fighting against several chronic illnesses. Numerous studies have reported that dietary components may have anti-inflammatory effects. Thus, research is required to examine the range of foods that may have the ability to alter the gene expression involved in inflammation (8). Excessive ROS disturbs the vital equilibrium of the intracellular redox state, causing oxidative stress as well as the depletion of the antioxidants. The balance between the rate of pro-oxidant (either exogenous or endogenous) generation, cellular enzymatic, and non-enzymatic antioxidants is determined by the intracellular redox state. Micronutrients are crucial to maintain human health; the scarcity of which may compromise the integrity of the genome (47).

Considering the relationship between genes and diet and their impact on inflammation, researchers have extensively explored variants that are present in specific genes*: ADIPOQ, CRP, TNF,* and *APOE*. These genes have become the focus of numerous studies, with scientists investigating their interactions with dietary factors across different populations. The *ADIPOQ* gene plays a crucial role in encoding the adiponectin protein. This protein is primarily secreted by adipose tissue but has far-reaching effects in various parts of the body, viz. muscle, liver, adipose tissue, hypothalamus, and vasculature cells. The adiponectin protein can act as an anti-inflammatory agent, an antioxidant, and an insulin sensitizer (48). Considering its significant role, researchers have observed a connection between reduced levels of adiponectin in the bloodstream and metabolic inflammation-related conditions encompassing metabolic syndrome, type 2 diabetes (T2D), and cardiovascular diseases (49).

CRP, known as C-reactive protein, is an acute-phase protein that serves as a significant marker for inflammation, and it is considered a critical indicator of cardiovascular risk (50). *CRP rs1205 T>C* SNP, which is present in the untranslated region 3′, has been related to the increased levels of CRP in the blood across various populations. In a clinical trial involving 1,584 US adults, researchers discovered that individuals with the CC homozygous genotype initially had higher levels of CRP in their plasma with respect to those carrying the T allele. However, after getting personalized healthy lifestyle advice, which includes 'Dietary Approach to Stop Hypertension' for 12 months, this difference in CRP concentration was not there (51). Similarly, a cross-sectional population-based study conducted in Brazil revealed that individuals carrying the T allele had reduced odds of experiencing low-grade systemic inflammation when their plasma content of highly unsaturated omega-3 fatty acids was above the median (52). These findings highlight the potential effect of genetic factors and lifestyle preferences on CRP levels and inflammation, emphasizing personalized health intrusions in the management of inflammation and cardiovascular risk.

In comparison to the other genes, the *APOE* gene does not directly produce a protein that is associated with inflammation. Instead, it produces the protein apolipoprotein E, which is primarily involved in lipid and lipoprotein metabolism. However, recent research has revealed some additional properties of apolipoprotein E, including anti-platelet aggregation, anti-inflammatory properties, and maintaining mitochondrial activity. The *APOE gene* has two single nucleotide polymorphisms (SNPs) - *rs7412 and rs429358* that cause alteration in the apolipoprotein E mRNA codons at positions 112 and 158, respectively. These modifications result in three possible protein isomeric forms: ε2, ε3, and ε4, depending on the resulting salt bridges. Among the six possible genotypic combinations, individuals carrying the *APOE* ε4 allele are at a greater risk of developing Alzheimer's disease, while those with the *APOE* ε2 genotype have been associated with long life (45). Studies have reported that *APOE* ε2 and ε3/ε3 genotypes are associated with increased plasma CRP (C-reactive protein) levels, and these genetic variations interact with dietary components with respect to inflammation. For instance, a clinical trial involving 176 British adults revealed that only *APOE* ε4 carriers exhibited a rise in plasma CRP after an eight-week high-saturated fatty acid diet. In another study from the UK, after 16 wk of dietary substitution with monounsaturated or omega-6 fatty acids against 9.5% of energy from saturated fatty acids, *APOE* ε4 carriers showed a decrease in plasma CRP concentration. However, *APOE* ε3/ε3 carriers displayed an increase in plasma CRP in the same intervention (53).

5.2.2. Diabetes

In recent years, the relationship between oxidative stress and Type 2 Diabetes Mellitus (T2DM) has gained significant attention from scientists who have been exploring the role of explicit genes, such as *NFE2 and NFE2L2,* which play a crucial role in the regulation of antioxidants proteins to fight against oxidative stress. Animal models have reported that *Nrf2* agonists have the potential to enhance insulin resistance, prevent obesity, and protect pancreatic beta-cells from apoptosis (54, 55).

PRKAA2, also known as *AMPK,* is another gene that plays a crucial role in inhibiting glucose, cholesterol, and triglyceride production by promoting fatty acid oxidation. Interestingly, *PRKAA2* and the *SIRT1* gene are interrelated. When *PRKAA2* is active, it leads to the activation of SIRT1, which in turn improves the substrate NAD+. The *SIRT1* gene is responsible for vital processes of deacetylation and controls the activity of several other genes. As a result, it controls the production of hepatic glucose, lipid metabolism, and insulin. It also deacetylates peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC-1), which suppresses the production of harmful reactive oxygen species (ROS) and regulates mitochondrial biogenesis. Studies have also reported that *SIRT1* can reduce hepatic glucose production by activating adenosine monophosphate-activated protein kinase *(AMPK)* through deacetylation (56).

Extensive research has been conducted and it was found that a combination of genetic factors and nutrition causes Nonalcoholic Fatty Liver Disease (NAFLD). Among these, the variation in the *PNPLA3 I148M* gene has been identified as a major contributor to NAFLD. Carriers of the *PNPLA3 I148M* gene are more prone to fat accumulation from dietary carbohydrates as carbohydrates can stimulate *PNPLA3* and inhibit the lipase. Genetic assessment can now detect this specific gene variation, thus assisting healthcare providers to offer personalized nutritional guidance to patients, which helps in the prevention NAFLD (19, 57).

5.2.3. Obesity

Over the past few decades, the growing concern over obesity has spiked the interest of researchers in understanding the role of specific genes that regulate the energy balance. Several specific genes have been identified to be associated with obesity, including *Melanocortin-4 receptor (MC4R),* leptin, and genes associated with carbohydrate and fatty-acid metabolisms (58). One such gene is the fat mass and obesity-associated gene *(FTO),* studies have revealed that certain alterations in the *FTO* gene can influence energy balance and body composition. Additionally, these genetic variations were found to interact with dietary factors, influencing adiposity characteristics and individual response to therapeutic interventions (59). In a study conducted by de Luis et al. (60), it was observed that variation in *APOA1 (rs670)* gene has significant effects on adiposity, cholesterol levels, and insulin resistance after following a 12-week hypocaloric diet (60). Another study identified a specific variant of the minor G allele of *MTIF3* causes more substantial weight loss after a four-year intervention program compared to the control group (61). The *MTIF3* gene is responsible for forming the initiation complex on the mitochondrial 55S ribosome which plays a critical role in essential biochemical pathways including energy balance and ATP synthesis. These research findings demonstrated the sophisticated relationship between genetics, diet, and health outcomes, offering valuable insights into potential personalized dietary approaches for individuals with specific genotypes. The promising data has potential implications in the development of personalized diet and weight loss programs in the future (62, 63).

5.2.4. Breast cancer

The *"BRCA1 susceptibility gene" (BRCA1, 17q21.31)* is responsible for fixing DNA damage and mutations, like breaks in the DNA strands, in conjunction with other cancer suppressors. The protein carries out various biological functions, such as controlling the cell cycle, transcribing DNA, maintaining genomic stability, tagging proteins for degradation, and regulating gene expression (64). Nikitina et al. (65) discovered that in individuals with *BRCA1* mutations, consuming coffee was associated with lower levels of micronuclei, indicating a preventive effect that may be mediated by increased biochemical activities involved in sensing and repairing DNA damage. Donovan et al. (66) also examined the impact of diet enriched with genistein using a mouse model and *in vitro* cell cultures. It was reported that genistein

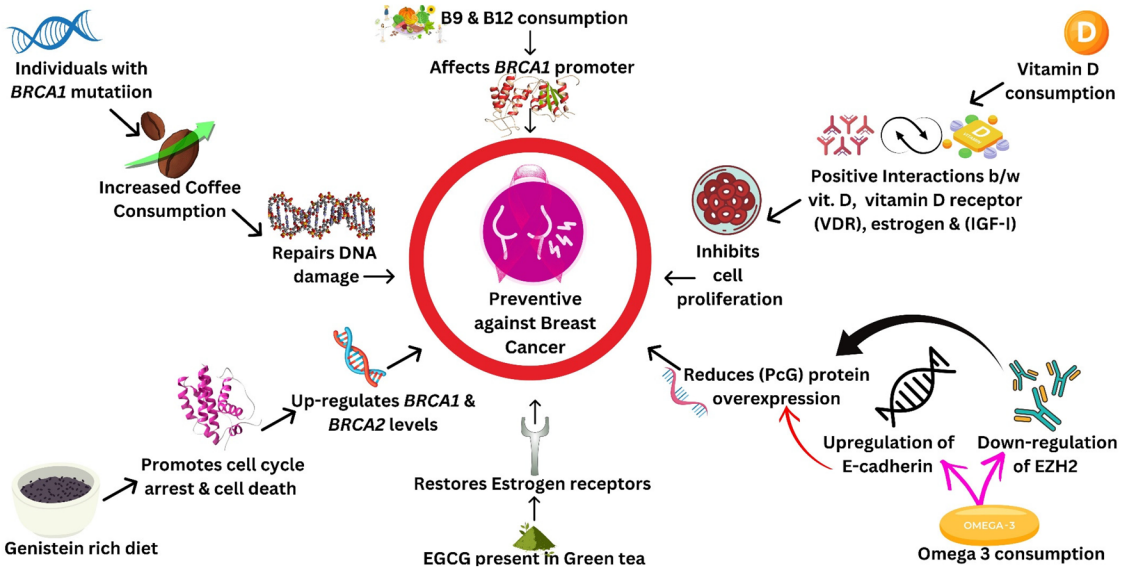

Figure 3. Mechanism of dietary components against Breast Cancer.

supplementation resulted in increased levels of *BRCA1* protein, reduced CpG methylation, and decreased binding affinity of the aryl hydrocarbon receptor (AHR) to *BRCA1 exon 1a*. From a molecular perspective, genistein appears to have multiple effects such as activating various DNA damage checkpoints leading to cell cycle arrest, mitotic catastrophe, and cell death (67). Furthermore, genistein finely modulates different angiogenesis pathways.

BRCA2 is another protein encoded by a gene found at 13q12.3 in our genetic code. *BRCA2* mutations can give rise to serious threats like Fanconi anemia, as well as various types of cancers (breast, ovarian, prostate, and pancreatic cancer). Alike *BRCA1*, genistein supplementation was found to be beneficial in the up-regulation of *BRCA2* levels and thus has a health-promoting effect (68).

Calcitriol ($1,25(OH)_2D$) plays a crucial role in various biological functions, including inhibiting cell proliferation, inducing differentiation and apoptosis, and suppressing angiogenesis in both normal and breast cancer cells. Epidemiological investigations have demonstrated an inverse correlation between the consumption of vitamin D and calcium and the density of mammographic breasts, along with extensive exposure to sunlight and reduced risk of BC (69). These correlations may be more pronounced in premenopausal women compared to postmenopausal women due to interactions between vitamin D, the vitamin D receptor (VDR), estrogen, and insulin-like growth factor-I (IGF-I) (Figure 3). Knight and colleagues (70), also reported that decreased risk of BC was associated with increased sun exposure, consumption of cod liver oil, and intake of milk in the age group of 10–19 years.

Estrogen Receptor-α (ER-α) plays an important role in the initiation and propagation stages of BC, as it increases the expression of oncoproteins while diminishing the levels of cell cycle inhibitors, like P21 (71). Dietary green tea polyphenol, epigallocatechin-3-gallate (EGCG), has the ability to revive ER-α expression in an in-vitro model and can also bring about a reorganization of the chromatin structure of the ER-α promoter through epigenetic alterations, including modified histone acetylation and methylation status, along with reduced binding of the transcription repressor complex at the regulatory region of the ER-α promoter (72), thus has a beneficial effect.

"The polycomb group protein" (Pcg protein) is an 'enhancer of zeste homologue 2′ (EZH2) and tends to be overexpressed in breast tumors and has a substantial correlation between its increased levels and the augmentation, proliferation, and dissemination of cancer (73). The incorporation of omega-3 polyunsaturated fatty acids (PUFAs) in the diet can have a crucial impact on regulating the levels of EZH2 within breast cancer cells (64).

5.2.5. CVDs

According to the World Health Organization, CVDs are the leading cause of death worldwide. These diseases include the occurrence of lesions in the arteries due to factors such as lipid accumulation, pus cells, blood cells, fibrosis, inflammatory response, and cell death. Eating a balanced diet is one critical factor that aids in both the treatment and prevention of cardiovascular disease. Through nutrition, the expression of genes associated with the biosynthesis of lipids, *Peroxisome proliferator, Fatty acid synthetase, lipoprotein lipase, arachidonate 5 lipoxygenase (ALOX5), and apolipoprotein E (APOE)* can be controlled. Variations in these genes can affect the susceptibility of an individual to CVD. The research found that heightened levels of the *ALOX5* gene have been observed in individuals with atherosclerotic lesions. Consumption of a diet rich in Polyunsaturated fatty acids can affect the expression of various factors involved in lipid and carbohydrate metabolism, leading to lower levels of low-density lipoprotein (LDL) cholesterol in patients who consumes essential fatty acids. In certain ethnic groups, such as African Americans, polymorphism in the hepatic *lipase gene (-504 cc)* can increase the levels of protective HDL cholesterol when on a high-fat diet. By influencing Membrane fluidity and through the generation of alternative ligands, polyunsaturated fatty acids can regulate genetic expression (66). Therefore, dietary interventions based on the genotype of an individual can be effective in the management of CVDs. The role of nutrigenetics/nutrigenomics in the prevention of obesity, type 2 diabetes mellitus, cancers, and cardiovascular diseases is reviewed in Table 1.

6. Nutrigenomics and personalized nutrition

Owing to the increased awareness of people about healthy eating practices, the concept of personalized nutrition has come into the limelight. In order to ensure a well-balanced diet, everyone needs to be aware of the quantity, quality, and variety of food because nutritional needs differ from person to person. However, genetic polymorphisms have an impact on an individual's perception of the relative significance of various nutrients. Numerous phytochemicals, including curcumin, resveratrol, genistein, and daidzein, function as transcription factor ligands and have the ability to directly affect gene expression. Dietary factors may affect one or more SNPs to reduce or increase the disease risk (8, 83). Obesity, one of the most serious complex conditions, results as a combination of genetic and lifestyle variables. Approximately, 120 genes have been linked to obesity including the *FTO gene*, which directly influences the use of medications, dietary intake, or physical exercise on body weight control (84). A well-balanced diet is therefore advised for obese individuals, with a primary focus on lean protein, whole grains, and moderate amounts of olive oil and dairy products (85).

Furthermore, the human defense system is regulated by various genes. For instance, human leukocyte antigen (HLA) genes play a vital role in antigen processing, T-cell activation, differentiation, immune response control, and antigen presentation (56). Individuals' varying immunological reactions to the same antigen are determined by the polymorphism of these genes (86). The immune system's capacity to function is significantly impacted by nutrient deficiency. For example, copper deficiency may lead to thymus atrophy and decreased antibody synthesis; iron deficiency leads to

Table 1. Relationship between nutrigenomics and prevention of NCDs.

Type of NCD	Genetic factor	Dietary intervention	References
Obesity	• Genetic factors account for 80% of the variation in twins' body mass indices (BMI). • Several genetic variations have been linked to BMI and obesity in genome-wide association studies. The single nucleotide polymorphism (SNP) *rs9939609* in the fat mass and obesity-associated gene (FTO) on chromosome 16 has the strongest relationship. • The A-allele of *rs9939609* has been linked to higher weight and BMI in many populations.	• Bioactive substances derived from food may affect human DNA. • The synthesis of inflammatory mediators during transcription is one of the main mechanisms for regulating gene expression and plays a critical role in obesity. • Bioactive compound α-tocopherol, works by reducing the extent of the persistent inflammatory process thus helping in the treatment of obesity.	(1, 4, 74, 75)
Cancer	• Deficiency of certain micronutrients can lead to rupturing of DNA double strand, oxidative lesions, or both contributing in the development of cancer. • Presence of certain molecules in contaminated food can produce toxic metabolites which interact with DNA, thus modifying its structure and causing mutations. • DNA mutations can cause severe damage to the liver, including necrosis, cirrhosis, and carcinoma.	• A diet deficient in folic acid can alter the process of DNA mutilations and can interfere on DNA replication, leading to an increased risk of cancer development. • Selenium, an important mineral, enhances the production of glutathione peroxidase enzyme that reduces the hydrogen peroxide thus, maintaining the integrity of cell membranes. • Similarly, zinc helps in the maintenance of genomic stability, genetic expression, and apoptosis modulation acting as a preventive strategy against the development of carcinoma.	(4, 76)
Diabetes	• According to genomic studies, type II diabetes risk is correlated with 65 SNPs. • The transcription factor 7-like 2 *(TCF7L2)* gene, which controls insulin secretion and sensitivity, is the key gene responsible for the disease's prevalence.	• Research based on nutrigenetics, and nutrigenomics is putting the spotlight on how foods, such as polyunsaturated fats, affect genes like *TCF7L2*. • The US Diabetes Prevention Program revealed in an intervention group of individuals, who adopted a healthier lifestyle by a reduction in their intake of total and saturated fat, increasing their fiber consumption, and engaging in moderate exercise, exhibited a reduced risk of developing type 2 diabetes with *TCF7L2 rs7903146* and *rs12255372* polymorphisms, indicating that lifestyle and dietary changes have the potential to influence genetic predispositions for diabetes.	(6, 77–79)
CVDs	• Genes such as *APOA1 and APOA5* are involved in the regulation of triglyceride levels by the modulation of lipoprotein lipase activity. • Diet can affect the expression of *APOE*, which further regulates the binding of lipid complexes to cell receptors.	• Fish oils and other sources of omega-3 polyunsaturated fats can reduce the risk of atherosclerosis by modulating several lipid metabolism-related genes, specifically *APOA1, APOA5, and APOE*. • Recent studies have demonstrated a relationship between low levels of vitamin D and a number of non-skeletal illnesses, including cancer, neurological disorders, metabolic diseases, and CVD. • A meta-analysis showed a linear and negative relationship between CVD risk and circulating vitamin D levels.	(80–82)

anemia, leukopenia, and decreased bactericidal activity; zinc deficiency results in immune deficiencies, leukopenia; and vitamin A deficiency (VAD) impairs mucosal barrier function and antibody reaction. Supplementation with vitamins C and E significantly accelerates antibody synthesis, the functioning of phagocytes, as well as the pace of T- and B-cell division (87). VAD is more likely to occur in people with mutations in the *BCMO1* gene (88).

7. Prospects and conclusion

It has become clear that nutrigenomics plays a major role in studying the effect of nutrients on the health of an individual. This can be thoroughly assessed by a variety of 'omic' technologies and biomarkers. In terms of their level of validation about health effects, some of these technologies are still in their infancy stage while others are much more developed. The genetic background, gender, and life stage can affect nutritional requirements; however, putting this knowledge into practice by formulating recommendations based on genotype or at the individual level is only feasible in just a few cases, where the effect of genotype clearly outweighs the impact of any other factor and is the primary determinant of an individual's nutritional and health status. Thus, it is necessary to combine nutrigenetic-based guidance with 'omic' biomarkers to test whether the personalized recommendation given produces the expected health benefit within the individual. Furthermore, it is crucial that geneticists, dieticians, and medical professionals receive proper training in the field of nutrigenetics/nutrigenomics so that their principles and practices are properly applied as nutrition has become progressively integrated with preventive medicine. A much more thorough comprehension of nutrient-gene interactions and their impact on phenotype is important to develop a personalized approach to nutrition for disease prevention. Incorporating nutrigenetics and nutrigenomics into public health recommendations carries some intrinsic risks. These include promoting a skewed perspective on the effect of genes on health and diluting general statements about healthy eating.

Although nutrigenomics holds enormous potential for preventing NCDs, there are several obstacles and restrictions standing in the way of their application in terms of both clinical practice and biomedical study. The American Heart Association emphasizes that there are several technical constraints, especially when it comes to planning and carrying out randomized clinical trials to create a solid body of knowledge for patient counseling. However, using biomarkers for food intake may help to mitigate this drawback. Furthermore, strict adherence to the diet can be difficult, and many nutritionists are opposed to a "one-size-fits-all"

approach to diets. But personalized nutrition helps to control, prevent, and treat a disease which can only be achieved with the help of the nutrigenomics field. In conclusion, a personalized diet can be a key component of achieving personalized healthcare, particularly in terms of leading a "good life."

Authors' contributions

PA: Writing- Original Draft, Writing- Review & Editing, Resources, Data Curation, Visualization; JK: Conceptualization, Methodology, Writing- Review & Editing, Visualization, Supervision; JS, PR, KS: Visualization, Supervision; VB, SK, VK: Supervision, Formal analysis.

Consent to participate

All the authors have read and approved the manuscript, and all are aware of its submission to the journal.

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