Polymorphisms, diet and nutrigenomics

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Summary

Every human being possesses an exclusive nutritional blueprint inside their genes. Bioactive food components and nutrients affect the expression of such genes. Nutrigenomics is the science that analyzes gene-nutrient interactions (nutrigenetics), which can lead to the development of personalized nutritional recommendations to maintain optimal health and prevent disease. Genomic diversity among various ethnic groups might affect nutrients bioavailability as well as their metabolism. Nutrigenomics combines different branches of science including nutrition, bioinformatics, genomics, molecular biology, molecular medicine, and epidemiology. Genes regulate intake and metabolism of different nutrients, while nutrients positively or negatively influence the expression of a number of genes; testing of specific genetic polymorphisms may therefore become a useful tool to manage weight loss and to fully understand gene-nutrient interactions. Indeed, several approaches are used to study gene-nutrient interactions: epigenetics, the study of genome modification not related to changes in nucleotide sequence; transcriptomics, the study of tissue-specific and time-specific RNA transcripts; proteomics, the study of proteins involved in biological processes; and metabolomics, the study of changes of primary and secondary metabolites in body fluids and tissues. Hence, the use of nutrigenomics to improve and optimize a healthy, balanced diet in clinical settings could be an effective approach for long-term lifestyle changes that might lead to consistent weight loss and improve quality of life.

Nutrigenomics

Nutrigenomics is an emerging field where advanced genomics tools are used to analyze the effects of nutrients on the genome and gene expression, and the effects of genetic variants on the intake of nutrients. The term “Nutrigenomics” was created to describe the interaction between nutrients and genes. Therefore, nutrigenomics links genetics to nutrition, physiology, biochemistry, metabolomics, proteomics, transcriptomics, and bioinformatics [1]. Nutrigenomics relies on three fundamental tenets:

• Genomic diversity in ethnic groups, which can affect bioavailability of nutrients and their metabolism;
• Choice of food and its availability based on cultural, geographical, and socio-economic factors;
• Malnutrition, which affects gene expression and poses a serious threat to genome stability by causing mutations in the DNA sequence or even chromosomal instability, that result in abnormal gene dosage and adverse phenotypes [2].

Therefore, nutrigenomics is the field of nutritional study that applies molecular techniques to exploring, analyzing, and understanding the physiological responses of particular populations or individuals to specific diets[3]. It further explains how dietary components might affect gene expression at pre-transcriptional, post-transcriptional, and translational levels, resulting in gain or loss of function of those particular proteins [3]. These, gene-nutrient interactions depend on the capacity of particular nutrients to bind with transcription factors, eventually regulating RNA polymerase recruitment to gene promoters and the ensuing transcript levels. For example, research on vitamin A, vitamin D and fatty acids indicate that these vitamins directly trigger the activation of nuclear receptors and induce gene transcription [4]. Furthermore, compounds like soy genistein and resveratrol from wine indirectly affect various molecular signaling pathways through nuclear factor kappa B, thereby activating and regulating major molecules linked with disease [1,5].

Recently, nutrigenetic studies have identified genetic variants associated with susceptibility to various diseases secondary to interaction with dietary factors. Theses scientific advancements will greatly contribute to the treatment and prevention of chronic disease, as they could potentially predict an individual’s risk, explain the etiology of the disease, and enable the personalization of nutritional management [6]. This scientific approach
may have caveats, as certain genes might preferentially favor the intake of some nutrients and adversely affect the consumptions of other beneficial nutrients [2, 7].

Nutrigenetics

Nutrigenetics encompasses the genetic variation effects on nutritional responses and nutrient function [2, 6]. Although nutrigenetics and nutrigenomics are closely related, these terms are not interchangeable. Nutrigenetics explores the effect of hereditary genetic variants on the uptake and metabolism of micronutrients, whereas nutrigenomics studies the interconnection between genome and diet with reference to nutritional effects on the metabolic, proteomic, transcriptional, and translation-al changes along with dietary variation due to an individual’s genetic background [8]. Recently, nutrigenetic research studies have enabled identification of genetic variants associated with disease susceptibility through interaction with specific dietary factors. For example, various genetic variants in genes involved in metabolic pathways affect the intake and usage of different micro-nutrients [2, 7, 9]. Nutrigenetic studies may be used to predict the risk of various chronic diseases, and, with the help of personalized nutritional management, these diseases could be prevented or better managed.

Gene-diet interactions are also involved in the response to nutritional interventions when limiting the total energy intake or altering the relative proportion of carbohydrates, proteins and fats. Studies have been performed in different populations to further explore the effects of genetic polymorphisms located near or within genes regulating food intake, lipoprotein and lipid metabolism, glucose homeostasis, insulin signaling, circadian cycles, inflammatory responses and amino acid metabolism on metabolic improvement, weight gain/loss, insulin resistance, and serum lipid levels. Most nutrigenetic tests analyze the effect of multiple polymorphisms on eating behavior changes. For instance, diets tailored to people with polymorphisms in the apolipoprotein E gene should decrease the intake of saturated fats compared to the standard dietary advice, because carriers of such polymorphisms are at increased risk of myocardial infarction (MI) [6, 10].

It is worth noting that not only DNA sequence variants are important, but also copy number variants. Some studies have reported the association between copy number variants (CNVs) for small genome sections and the risk of metabolic diseases, as illustrated in the following three examples: 1) copy number variants of the leptin receptor gene are linked with metabolic traits and with type 2 diabetes mellitus risk [11]; 2) lower copy number of the salivary amylase alpha 1A gene has been associated with obesity predisposition, thereby linking obesity to carbohydrate metabolism [12]; 3) a pentanucleotide (CTTTA) deletion/insertion in the 3′-untranslated region of the leptin receptor gene has been associated with type 2 diabetes mellitus risk [13]. Additional studies are needed to further explore the many levels of gene-diet interactions in relation to disease risk and dietary response [6].

Nutritional epigenetics

Epigenetics involves reversible and heritable processes that regulate the expression of genes without associated changes in the coding sequence of DNA. In fact, epigenetic dysregulation may underlie the onset of various chronic diseases and their progression [14]. Complex interactions between nutrients and DNA methylation, noncoding RNAs, and covalent histone modifications contribute to obesity, type 2 diabetes mellitus, dyslipidemia, cardiovascular diseases, non-alcoholic fatty liver disease, and cancer. For example, diets rich in fats and sugar are associated with abnormal methylation patterns of neuropeptide genes that control food intake and could be involved in obesity development [15]. Similarly, low-protein diets could alter lipid and glucose levels by disrupting histone modifications within major regulatory genes [16]. Moreover, deficiency of various micro-nutrients – like vitamin A, group B vitamins, selenium, potassium, and iron – are linked with hypermethylation of tumor suppressor genes that play a crucial role in cancer [6, 16].

Nutriepigenetics is the study of nutritional interventions that alter epigenetic changes which significantly impact treatment and prevention of chronic diseases. For example, it has been demonstrated that the anti-inflammatory effects of the Mediterranean diet are linked to inhibitory hypermethylation of proinflammatory genes [17, 18]. Furthermore, polyunsaturated fatty acid administration positively regulates expression of specific miRNAs that inhibit lipogenic and oncogenic genes [19]. Curcumin is also an important epigenetic regulator that exerts protective effects against heart failure and liver injury through the regulation of specific DNA methylation and histone modification patterns. These data suggest that introducing specific dietary compounds to an individual’s diet, that modulate epigenetic patterns, could be an efficient strategy for reducing the prevalence of obesity and associated comorbidities [6, 20].

Nutritional transcriptomics

Transcriptomics is the process that evaluates the sequence and abundance of all RNA transcripts at a specific time point. RNA levels are tissue-specific and time-specific. During the process of transcription, activated transcription factors move to the nucleus, where they bind to a specific DNA sequence within the promoter region of a particular gene and inhibit or facilitate that gene’s transcription. Transcription factors can also be stimulated by physiological signals triggered by bioactive food components, nutrients or their metabolites, hormones, diseases, and pharmacological treatments. Therefore, transcription factors act like sensors and thereby modulate transcription. Transcriptomics can provide information on the mechanisms
related to a specific nutrient or diet. Transcriptional changes also help in the identification of genes, metabolites, or proteins that alter pre-disease states and assist in distinguishing and characterizing bioactive food components or nutrient-regulated pathways [1, 21, 22].

**Nutritional proteomics**

Proteomics identifies the complex array of proteins involved in biological processes, i.e., the proteome. Various pathological or physiological states can alter the proteome [21, 22].

Proteomics uses a variety of technologies designed to analyze protein expression including electrophoresis, organelle proteome analysis, high throughput extract pre-fractionation screening and mass spectrometry [3, 21]. Proteomics serves as a biological tool to fully understand genome activation in response to specific nutrients. For example, butyrate can change the expression of different proteins belonging to the ubiquitin proteasome system. This suggests that butyrate regulates major proteins that control cell differentiation, cell cycle, and apoptosis by proteolysis [1, 22, 23]. Proteomics can thereby identify pathways that are important in various disease states including those related to nutrition.

**Nutritional metabolomics**

Metabolomics is the branch of functional genomics that identifies primary and secondary metabolites in bodily fluids and can be used to understand alterations in metabolites and the mechanisms to isolate and characterize them. Metabolomics is a significant tool for investigating the effect of food on the health of individual. Identification of the food-derived biomarkers helps in understanding the variability among individual to metabolize the same foods during healthy as well as in diseased states. Nutritional metabolomics identifies the metabolic changes caused by specific nutrients or diets [21, 24, 25].

It also involves the study of metabolism under various genetic and environmental stresses [1, 21, 26, 27]. Food components and nutrients interact and alter metabolic pathways in different ways. Many cohort studies have identified the intake biomarkers like red meat, fish, walnuts and whole-grain bread. Under specific organic stimulations the monoterpane called perilla alcohol, extracted from strawberries, could behave as an anticancer molecule [24]. Similarly, Wittenbecher et al. [28], applied serum metabolomics to reveal the significant association of various red meat intake biomarkers with type-2 diabetes risk.

**Precision nutrition**

Nutrigenetics can be used to personalize diets by modifying them according to individual genetic variation. Precision nutrition is an important part of precision medicine, which consists of establishing guidelines for nutritional requirements of particular subgroups of people [6, 29, 30]. For example, lactose intolerance, phenylketonuria, or celiac disease are managed via tailored nutritional instructions based upon the genetic background [29].

Numerous SNPs are linked with chronic diseases because of their interaction with the intake of micro- and macronutrients or by specific foods or diets. For instance, polymorphisms of taste perception genes, including the sweet taste receptor TAS1R2 (Taste 1 Receptor Member 2) gene and CD36 gene, were reported to be linked with dyslipidemia among research participants in Mexico with high consumption of carbohydrates and fats, respectively [31, 32]. Similarly, common variants of homocysteine metabolism-regulating genes, such as MTHFR (methylene tetrahydrofolate reductase) and MTR (methionine synthase), have been associated with increased breast cancer risk in individuals with reduced intake of vitamin B6, vitamin B12, and folate [33]. Interestingly, SNPs in the VDR (vitamin D receptor) gene affect the availability of vitamin D and are known to be associated with osteoporosis predisposition in postmenopausal females with reduced calcium intake [6, 34].

In clinical practice, nutrigenetics is currently being used to evaluate the genes involved in the transport and metabolism of nutrients, toxins removal, and protection against oxidative stress. Therefore, polymorphisms in these genes are included in nutrigenetic tests to evaluate their effects on eating habits. For instance, personalized diets designed according to specific ACE (angiotensin I converting enzyme) genotypes may recommend higher sodium intake compared to the standard population-based dietary advice [6, 10, 35].

**Nutritional effects on gene expression profiles**

Nutrition influences health outcomes by affecting expression of genes that regulate crucial metabolic pathways. Western dietary patterns – rich in processed grain products, processed meats, sweets, and desserts – have a gene expression profile typical of cancer signaling and inflammatory response. This is not the case in individuals that eat whole grain products, fruits, and vegetables. Pathway analyses have shown that higher meat consumption is linked to genetic networks associated with colon cancer [36]. Moreover, higher saturated fatty acid consumption results in a gene expression profile that is typical of glucose intolerance, liver lipid accumulation, inflammation, and increased neuropeptide expression, leading to development of obesity. On the contrary, lower protein diets increase the expression of hepatic gluconeogenic genes, with subsequent glucose intolerance. Furthermore, diets lacking folate and choline are linked with dysregulation of lipid metabolism genes, thus predisposing to non-alcoholic fatty liver disease [37]. Similarly, chromium deficiency induces downregulation of insulin signaling genes, which may lead to type 2 dia-
betes mellitus. Selenium, vitamin A, and vitamin B12 deficiencies increase the susceptibility to cardiovascular diseases by upregulating lipogenic and proinflammatory genes [6]. Research studies have also reported favorable effects of bioactive food components and nutrients on gene expression profiles; for example, people consuming the Mediterranean diet have lower postprandial expression of genes encoding proteins involved in inflammation, oxidative stress, atherogenesis, and endoplasmic reticulum stress-related activation. Furthermore, a higher intake of monounsaturated fatty acids through olive oil consumption is linked with reduced expression of inflammatory and lipid storage genes. Consumption of higher polyunsaturated fatty acid-containing diets positively regulates the expression of neuropeptide genes that modulate energy homeostasis [38, 39]. Bioactive food components like theaflavin, epigallocatechin-3-gallate, genistein, curcumin and sulforaphane exhibit anticancer properties by upregulating tumor-suppressor genes and downregulating proto-oncogenes. In addition, resveratrol and curcumin have antiatherogenic effects by downregulating the expression of matrix metalloproteinases that cause the formation and progression of plaques. Finally, apple polyphenols prevent diet-induced obesity by regulating genes involved in fatty acid oxidation, lipolysis, and adipogenesis [15, 40].

**Genetic polymorphism effect on dietary intake**

Genome-wide association studies have evaluated genetic polymorphisms associated with various metabolic pathways [2]. Epidemiological and interventional studies have also explored the associations of genetic variants with dietary intake [41]. For example, clinically significant associations have been reported between: 1) the APOA2 (c.2265T>C) variant and intake of saturated fatty acids and body mass index, 2) MTHFR variants and homocysteine levels, and 3) CYP1A2 variants and caffeine-related hypertensive response [2, 42, 43]. Inborn errors of metabolism are caused by mutations in specific genes encoding key metabolic enzymes. These pathogenic variants lead to gene-diet interactions altering nutritional requirements and metabolism: classical examples are lactose intolerance and phenylketonuria. The T>C-13910 variant upstream of the lactase gene (LCT) results in non-persistence or absence of the lactase enzyme after infancy, therefore individuals with this variant do not digest lactose. On the other hand, phenylketonuria is an autosomal recessive disorder caused by mutations in the phenylalanine hydroxylase (PAH) gene, a major hepatic enzyme that is responsible for the conversion of phenylalanine to tyrosine [2, 44, 45]. Other genetic-food interactions are much more complex, such as polygenic interactions underlying the multifactorial etiology of cancer, obesity, type 2 diabetes, and cardiovascular disease. Such diseases derive from the interaction among several genes and environmental factors, and respond to numerous dietary exposures. For example, a number of genetic variants are associated with an increased obesity risk, such as those found in the FTO gene, UCP1 and UCP3 genes, the PPAR (peroxisome proliferator-activated receptor) encoding genes, the melanocortin 4 receptor (MC4R), and the leptin receptor (LEPR) gene [2, 46, 47], as detailed in Table I. In coronary artery disease, variants in genes associated with lipid metabolism, such as LPL (lipoprotein lipase), CETP (cholesteryl ester transfer protein), LDLR (low density lipoprotein receptor), and APOE (apolipoprotein E), affect the intake and catabolism of cholesterol and other lipids, resulting in atherosclerosis (Tab. I) [2, 48, 49]. Further studies evaluated the role of the genetic variants in the CYP1A2 (Cytochrome P450 1A2) gene, which encodes the main caffeine-metabolizing enzyme, in cardiovascular disease. A higher consumption of caffeine might be linked with increased cardiovascular disease risk in subjects with genetic variants associated with “slow” caffeine metabolism. On the other hand, people that have genetic variants associated with fast caffeine metabolism are protected from the effects of moderate caffeine consumption [2, 50]. Genetic variations of the APOA2 (apolipoprotein A2) gene are associated with obesity via alterations in energy intake. Chinese and Asian-Indian populations with a specific APOA2 variant are at a greater risk of developing obesity when consuming food rich in saturated fatty acids, but with lower saturated fatty acids intake, such risk was not observed. Similar studies were performed among Mediterranean populations of Southeastern Spain. Moreover, polymorphisms of genes associated with iron, vitamin C, vitamin D, and vitamin B12 metabolism have been reported to affect the risk of deficiency or reduced levels of these nutrients [51, 52]. Other genetic loci were analyzed for their associations with the intake of macronutrients. Merino et al. [53] identified two genetic loci, DRAM1 (DNA damage regulated autophagy modulator 1) and RARB (retinoic acid receptor beta), which exhibited a genome-wide significant association with macronutrient intake. Additionally, they also confirmed the association of the FGF21 (fibroblast growth factor 21) genetic variant (rs838133) with the intake of macronutrients [41, 53].

**Genetic polymorphisms associated with body weight**

Research studies have identified significant associations between genetic variants and body weight. Numerous genetic loci have been linked to weight loss following hypocaloric diets and physical activity. These genes encode important enzymes regulating adipogenesis, lipid metabolism, the circadian clock, carbohydrate metabolism, appetite control, energy intake and expenditure, cell differentiation, and thermogenesis [54, 55]. Moreover, genetic variants associated with taste- and texture-related, and olfactory genes could affect individual preferences and sensitivity towards certain foods, influ-
Tab. I. Genetic polymorphisms, their related genes, and involved dietary factors if known, and putative disease risks.

| Gene     | Polymorphism | Putative disease risks | Effect |
|----------|--------------|------------------------|--------|
| TAS1R2   | rs35874116   | Hypertriglyceridemia   | Carbohydrate responsiveness |
|          | ile191Val    |                        |        |
| CSHMT    | L474F        | Colon cancer           | Folate degradation          |
|          |              | Neural tube defects    |        |
| MTHFR    | rs1801133    | Breast cancer          | Increased folic acid intake|
|          |              | Homocystinuria         | Macronutrient intake        |
|          |              | Cardiovascular diseases| High levels of homocysteine|
|          |              | Diabetes               | Folate metabolism           |
|          | C677T        | Neural tube defects    |        |
|          | A1298C       |                        |        |
|          | A222V        |                        |        |
| MTHFD1   | R653Q        | Neural tube defects    | Higher folate intakes       |
| MTR      | rs1905087    | Breast cancer          | Lower folate concentration  |
|          | A2756G       |                        |        |
| MTRR     | A66C         | Neural tube defects in  | Lower folate concentration  |
|          |              | offspring              |        |
| VDR      | rs1544410    | Osteoporosis           | Affects vitamin D levels    |
|          | T>C          | Prostate cancer        |        |
|          | rs11568820   |                        |        |
| APOA1    | rs670        | Metabolic syndrome     | -      |
|          | rs5089       |                        |        |
| APOA2    | rs5082       | Cardiovascular diseases| Higher total energy, fat,   |
|          |              | Obesity                | and protein intake          |
| APOA5    | rs964184     | Higher risk of early heart attacks | Greater reduction in TC and LDL-c |
|          | rs662799     | Lipid metabolism       | Macronutrient intake        |
|          |              | disturbances           |        |
|          |              | Less weight gain on high fat diets |        |
| APOB     | rs512535     | Metabolic syndrome     | Low Fat                       |
| APOC3    | rs5128       | Metabolic syndrome     | Cholesterol metabolism      |
|          | C 3175G      |                        |        |
| APOE     | rs429358     | Lipid metabolism       | Macronutrient intake        |
|          | rs7412       | disturbances           |        |
|          |              |                        |        |
| PNPLA3   | rs739409     | NAFLD                  | -      |
| CYP1A1   | TMsp1C       | Breast and prostate cancer | Oxidative metabolism of estrogens |
|          | lle462Val    |                        |        |
| CYP1A2   | A>C          | Heart diseases         | Reduced ability to metabolize caffeine |
| CYP1B1   | C194G        | Congenital glaucoma    |        |
| CYP2R1   | rs10741657   | Lower vitamin D levels | Increased consumption of food rich in vitamin D |
|          | rs10766197   |                        | Increased sun exposure       |
| CYP17A   | T54C         | Congenital adrenal hyperplasia | Increased estrogen level |
| FTO      | rs9939609    | T2DM                   | Macronutrient intake        |
|          |              | Obesity                |        |
| FTO      | rs8050136    | T2DM                   | Macronutrient intake        |
|          |              | Obesity                |        |
|          | rs1558902    | Obesity                | Greater weight loss         |
|          |              |                        | Less reductions in insulin and HOMA-IR |
| MC4R     | rs17782313   | T2DM                   | Increased BMI               |
| MC4R     | rs12970134   | Metabolic syndrome     | Macronutrient intake        |
| TCF7L2   | rs7903146    | T2DM                   | Smaller weight loss and HOMA-IR |
| LCT      | rs4988255    | Metabolic syndrome     | Macronutrient intake        |
|          |              | Obesity                |        |
| PPARA    | rs1800206    | Lipid metabolism       | Macronutrient intake        |
|          | rs60008259   | disturbances           | Low n-6 Fatty Acid          |
|          |              | Hypercholesterolemia   |        |
| Gene     | Polymorphism | Putative disease risks                                           | Effect                                      |
|----------|--------------|-----------------------------------------------------------------|--------------------------------------------|
| PPARG    | rs1801282    | Obesity, Insulin Sensitivity                                      | Macronutrient intake                       |
| TXN      | rs2301241    | Abdominal obesity                                                |                                            |
| GIPR     | rs2287019    | Cardiovascular diseases                                          | Greater weight loss                        |
|          |              |                                                                  | Greater decreases in glucose, insulin and HOMA-IR |
| DHCR7    | rs12785878   | Vitamin D insufficiency                                          | Greater decreases in insulin               |
|          |              |                                                                  | HOMA-IR                                    |
| LIPC     | rs2070895    | Lipid metabolism disturbances                                    | Higher decreases in TC and LDL-c           |
|          | rs1800588I   |                                                                  | Lower increase in HDL-c                    |
| PPM1K    | rs1440581    | Maple syrup urine disease                                        | Less weight loss                           |
|          |              |                                                                  | Lower decreases in insulin and HOMA-IR     |
| TFAP2B   | rs987237     | Non-familial congenital heart disease, Char syndrome              | Higher weight regains                      |
| IRS1     | rs2943641    | Autism spectrum disorder, Hepatocellular carcinoma               | Greater decreases in insulin, HOMA-IR, weight loss |
| PCSK1    | rs6232       | Higher obesity and insulin sensitivity risk                       |                                            |
| PCSK7    | rs256918     | Metabolic disorders, Liver diseases                              | Higher decreases in insulin and HOMA-IR    |
| MTNR1B   | rs10830963   | Type 2 Diabetes, Impairment of early insulin response             | Lower weight loss in women                 |
| IL-1A    | G4845T       | Chronic inflammatory diseases, Periodontitis, Coronary artery disease, A few autoimmune diseases and cancers | Increased IL-1 plasma concentrations       |
|          | C-889T       |                                                                  |                                            |
| IL-1B    | C 3954T      | Chronic inflammatory diseases, Periodontitis, Coronary artery disease, A few autoimmune diseases and cancers | Increased IL-1 plasma concentrations       |
|          | A -511G      |                                                                  |                                            |
| IL-1RN   | C 2018T      | Chronic inflammatory diseases, Periodontitis, Coronary artery disease, A few autoimmune diseases and cancers | Increased IL-1 plasma concentrations       |
| IL-6     | rs2069827    | Low-grade chronic inflammation, Obesity, Visceral fat deposition, Insulin resistance, Dyslipidemia, Risk for cardiovascular diseases | Lower weight gains, Tissue healing         |
|          | G -174C      |                                                                  |                                            |
| IL6R     | A>G          | Low-grade chronic inflammation                                   | Tissue healing                             |
| SH2B1    | rs7498665    | Obesity, Type 2 diabetes                                          | Higher fat intake                          |
| SLC2A2   | rs5400       | Diabetes                                                         | Higher sugar consumption                  |
|          |              |                                                                  | Insulin sensitivity                        |
| F2       | rs1799963    | Higher risk of thrombosis and cerebral stroke                     |                                            |
| F5       | rs6025       | Higher risk of thrombosis                                         |                                            |
| FUT2     | rs602662     | Lower vitamin B12 levels                                          | Increased consumption of Food rich in vitamin B12 |
|          | Gly258Ser    |                                                                  |                                            |
| Gene     | Polymorphism | Putative disease risks                                                                 | Effect                                      |
|----------|--------------|----------------------------------------------------------------------------------------|---------------------------------------------|
| ALPL     | rs4654748    | Lower Vitamin B6 blood concentration                                                   | Increased consumption of food rich in vitamin B6 |
| CBS      | rs1801181    | Colorectal Cancer                                                                      |                                             |
|          | rs121964962  | Homocystinuria                                                                         |                                             |
|          | rs2802292    | Vitamin deficiency                                                                     |                                             |
|          | rs2802288    | Dementia                                                                               |                                             |
|          | rs3740051    | Heart disease                                                                          |                                             |
|          | rs2236519    | Stroke                                                                                 |                                             |
|          | rs2272773    |                                             |                                             |
| FOXO3    | rs2802292    | Longer lifespan                                                                         |                                             |
| CBS      | rs3740051    | Higher basal energy expenditure                                                        |                                             |
|          | rs2236519    |                                             |                                             |
|          | rs2272773    |                                             |                                             |
| PEMT     | rs12525817   | Low choline                                                                            | Increased choline intake                    |
| PLIN1    | rs894160     | Obesity                                                                                | Macronutrients intake                      |
| CBS      | rs1260326    | Lipid metabolism disturbances                                                          | Macronutrients intake                      |
| CBS      | rs4959853    | Lipid metabolism disturbances                                                          | Macronutrients intake                      |
| CBS      | rs328        | Lipid metabolism disturbances                                                          | Macronutrients intake                      |
| CBS      | C1595G       | Lipid metabolism disturbances                                                          | Macronutrients intake                      |
| CBS      | rs12740374   | Lipid metabolism disturbances                                                          | Macronutrients intake                      |
| CBS      | rs4580704    | Lipid metabolism disturbances                                                          | Coronary heart disease                     |
| CBS      | rs5874116    | Lipid metabolism disturbances                                                          | Type 2 diabetes                            |
| CBS      | rs9701796    | Lipid metabolism disturbances                                                          | Type 2 diabetes                            |
| CBS      | rs307355     | Lipid metabolism disturbances                                                          | Dental caries                              |
| CBS      | rs35744813   | Lipid metabolism disturbances                                                          | Reduced promoter activity                   |
| CBS      | rs307377     | Lipid metabolism disturbances                                                          | Dental caries                              |
| CBS      | rs846664     | Association with the aging process                                                     | Alcohol dependence                         |
| CBS      | rs978739     | Association with the aging process                                                     | Alcohol dependence                         |
| CBS      | rs713598     | Metabolic diseases                                                                     | Bitter taste of PTC or PROP perception     |
| CBS      | rs7172866    | Coronary heart disease                                                                  |                                             |
| CBS      | rs10246939   | Risk of hypertension                                                                   |                                             |
| CBS      | rs239345     | Risk of hypertension                                                                   |                                             |
| CBS      | rs11064153   | Risk of hypertension                                                                   |                                             |
| CBS      | rs578568     | Risk of hypertension                                                                   |                                             |
| CBS      | rs239345     | Risk of hypertension                                                                   |                                             |
| CBS      | rs4401050    | Risk of hypertension                                                                   |                                             |
| CBS      | rs4790522    | Cardiovascular risk disease                                                            |                                             |
| CBS      | rs8065080    | Risk of hypertension                                                                   |                                             |
| Gene     | Polymorphism | Putative disease risks                                      | Effect                                      |
|----------|--------------|-------------------------------------------------------------|---------------------------------------------|
| CD36     | rs1761667    | Hypercholesterolemia, Metabolic syndrome, Type 2 diabetes mellitus | Ethnic-specific effects                     |
|          | rs1984112    | Lipid metabolism, Type 2 diabetes, Cardiovascular disease risk |                                             |
|          | rs1527483    | Obesity                                                     |                                             |
|          | rs2151916    | Obesity, High triglycerides levels                           |                                             |
|          | rs7755       | Type 2 diabetes mellitus                                    |                                             |
|          | rs1049673    | Obesity, Hypertension, Type 2 diabetes mellitus, Premature coronary heart disease |                                             |
|          | rs3840546    | Obesity, Type 2 diabetes mellitus                            |                                             |
|          | rs3211933    | Metabolic syndrome                                          |                                             |
|          | rs10499859   | Metabolic syndrome                                          |                                             |
|          | rs3211867    | Obesity                                                     |                                             |
|          | rs3211883    | Metabolic syndrome                                          |                                             |
|          | rs3173798    | Obesity, Metabolic syndrome                                  |                                             |
|          | rs3211892    | Obesity, Metabolic syndrome                                  |                                             |
|          | rs1358337    | Metabolic syndrome                                          |                                             |
|          | rs1054516    | Metabolic syndrome, High levels of triglyceride              |                                             |
|          | rs1049654    | Metabolic syndrome                                          |                                             |
|          | rs3211909    | Metabolic syndrome                                          |                                             |
|          | rs3211849    | Metabolic syndrome, High levels of triglyceride              |                                             |
|          | rs1358337    | Metabolic syndrome                                          |                                             |
|          | rs1194197    | Metabolic syndrome                                          |                                             |
|          | rs11760281   | Metabolic syndrome                                          |                                             |
| OR7D4    | rs61729907   | Metabolic syndrome                                          |                                             |
| OR11H7P  | rs1953558    | Obesity, Dental caries, Diabetes, Cardiovascular disease, Hypertension, Hyperlipidemia, Cancer |                                             |
| OR6A2    | rs72921001   | Gestational choriocarcinoma                                  |                                             |
| LEPR     | rs3790483    | Obesity, Metabolic syndrome                                  | Low n-6 PUFA, High n-3 PUFA                 |
| POMC     | rs713586     | Obesity, Early-onset type 2 diabetes                         |                                             |
| BDNF     | rs6265       | Obesity, Psychological eating disorders                      | Carbohydrate and fat intakes                |
| KCNB1    | rs6063399    | Obesity                                                     | Lower BMI                                   |
| KCNC2    | rs7511660    | Obesity                                                     | Lower BMI                                   |
| Gene          | Polymorphism | Putative disease risks                                                                 | Effect                                      |
|---------------|--------------|----------------------------------------------------------------------------------------|---------------------------------------------|
| TMPRSS6       | rs1421312    | Anemia                                                                                 | Iron deficiency                            |
|               | rs2111833    | Damage of immune function, work performance, and damage of adolescent's psychological behavior and mental development |                                             |
| TUB           | rs2272382    | Obesity                                                                                | Higher consumption of mono- and disaccharides |
|               | rs1528133    |                                                                         | Higher glycemic load                        |
| CAPN10        | SNP-44       | Type 2 diabetes mellitus                                                               | Total cholesterol                           |
| ACE           | Insertion/Deletion (I/D) | Type 2 diabetes mellitus Acute myocardial infarction Hypertension | Salt sensitivity                            |
| ADRB2         | Arg16Gly     | Asthma                                                                                 | Carbohydrate responsiveness                |
|               | Glu27Glu     | Chronic obstructive pulmonary disease                                                  |                                             |
| ADRB3         | Trp64Arg     | Coronary heart disease Weight gain                                                     |                                             |
|               |              | Type 2 diabetes mellitus                                                               |                                             |
| PON1          | rs854549     | Cardiovascular disease                                                                 | Detoxification/Oxidative stress Lipid levels |
|               | rs854552     | Atherosclerosis                                                                       |                                             |
| Cdx-2         | G3751A       | Vitamin D deficiency                                                                  | Calcium intestinal absorption Increasing bone mineral density |
| CYP24A1       |              | Vitamin D deficiency                                                                  |                                             |
| GSTM1         | Insertion/Deletion | Vitamin C deficiency Cancer Coronary artery disease Atopic asthma | Low vitamin C intake                        |
| GSTP1         | A313G        | Ascorbic acid deficiency                                                               | Low vitamin C intake                        |
| HFE           | C282Y        | Iron-storage disease                                                                  | Iron metabolism                             |
|               |              | Iron overload                                                                         |                                             |
| ADH1B         | 47His        | Alcohol dependence                                                                    | Systemic ethanol clearance                 |
|               | 569Arg       |                                                                         |                                             |
|               | rs1229984    |                                                                         |                                             |
| ADH1C         | 349Ile       |                                                                         |                                             |
| ALDH2         | E487K        | Alcohol metabolism                                                                    | Acetaldehyde accumulation Alcohol metabolism |
|               | rs671        |                                                                         |                                             |
| FADS1         | rs174557     | Abnormal lipid profile                                                                 | PUFA metabolism                            |
|               | rs174546     |                                                                         |                                             |
| AGT           | T>C          | Hypertension                                                                          | Salt sensitivity Increased blood flow and respiration |
|               | M235T        | Cardiorespiratory disorders                                                           |                                             |
| MCM6          | C 13910T     | Lactose intolerance                                                                   |                                             |
| HLA           | DQ2/DQ8      | Celiac disease                                                                        | Gluten intolerance                          |
| BCO1          | Ala579Val    | Hypercarotenemia Vitamin A deficiency Chronic lung disease                            | Vitamin A Higher levels of provitamin A carotenoids |
| GSTT1         | Insertion / Deletion | Serum ascorbic acid deficiency Free radical production   |                                             |
| MnSOD         | Ala16Val     | Breast cancer                                                                         | Reduced oxidation of catecholamines         |
| TNF-A         | G -308A      | Obesity Insulin resistance Dyslipidemia                                               | Whole body glucose homeostasis alteration   |
| Gene  | Polymorphism | Putative disease risks | Effect |
|-------|--------------|------------------------|--------|
| CRP   | rs1205       | Mental health disorder  |        |
|       | G>A          | Depressive disorder     |        |
|       |              | Low-grade chronic       | Higher levels of CRP |
|       |              | inflammation            |        |
| SULT1A1 | G638A       | Post-menopausal breast  |        |
|       |              | cancer                  |        |
|       |              |                          |        |
| NQO1  | C609T        | Cancer                  |        |
|       |              |                         |        |
| FACTOR V | G1691A    | Deep venous thrombosis  |        |
|       |              |                         |        |
| MMP1  | 1G/2G        | Accelerated skin aging  |        |
|       |              |                         |        |
| COL1A1 | Sp1 G>T     | Accelerated skin aging  | Mature connective tissue structure, essential for tensile strength |
|       |              |                         |        |
| COL5A1 | BstUI C>T   | Achilles tendinopathy   | Increase in content of type V collagen |
|       |              | Anterior cruciate ligament rupture | Decrease in fibril diameter and biomechanical properties of tendons |
|       |              | Tennis elbow            |        |
| GPX1  | C>T          | Premature aging         | Protect against oxidative stress |
|       |              | Prostate cancer         |        |
|       | rs713041     | Colorectal cancer       | Lymphocyte GPx activities |
|       |              |                         |        |
| GPX4  | C -262T      | Premature aging         | Protect against oxidative stress |
|       |              |                         |        |
| CAT   | rs1051740    | Cellular damage         | Process toxins and pollutants |
|       |              | Accelerated aging       |        |
|       | rs7852552    | Non-goitrous congenital hypothyroidism | Increased lean body mass |
|       | rs16892496   |                          |        |
| EPHX1 | rs4532       | Addictive behavior      | Regulate neuronal growth and development |
|       | G-94A        |                          | Mediate some behavioral responses |
|       |              | Chronic kidney disease  |        |
|       |              | Chronic obstructive pulmonary disease |        |
|       |              | Metabolic disease       |        |
|       | rs1800497    | Compulsive and risk- seeking behaviors | Carbohydrate responsiveness |
|       | Taq1A/2A     | Increased risk for co-morbid substance use disorders (alcoholism & opioids) | Reduced carbohydrate intake |
|       |              | Binge eating behavior   |        |
|       |              | Addictive disorder      |        |
|       | Ser9Gly      | Addictive behavior      | Cognitive, emotional, and endocrine functions |
|       |              |                          |        |
| DRD4  | C521T        | ADHD                    |        |
|       |              | Opioid dependence       |        |
|       |              | Novelty seeking         |        |
|       | Trp64Arg     | Obesity and bodyweight-related disorders | Exercise responsiveness |
|       | K153R        | Skeletal muscle-related disorders |        |
|       | rs5859       | Lung cancer             |        |
|       | rs7579       | Inflammation Cancer     | Selenium availability and metabolism |
| Gene      | Polymorphism | Putative disease risks                                      | Effect                          |
|-----------|--------------|-------------------------------------------------------------|---------------------------------|
| BCMO1     | rs1293492    | Vitamin A deficiency                                        | Low vitamin A levels            |
|           | rs7501351    |                                                             |                                 |
| SOD2      | rs4880       | Breast and prostate cancers                                 |                                 |
| ACSL1     | rs9997745    | Metabolic Syndrome                                          |                                 |
| DNMT3B    | rs6087990    | Colorectal cancer Adenoma                                   | High folate                     |
|           | rs2424913    |                                                             |                                 |
|           | rs2424909    |                                                             |                                 |
| ADAM17    | rs10495563   | Obesity                                                     | Low n-6 fatty acids              |
| FAF1      | rs3827730    | Alcohol dependence                                          |                                 |
| CSK       | rs1378942    | Hypertension                                                |                                 |
| Intergenic| rs2168784    | Alcohol dependence                                          |                                 |
| NADSYN1   | rs75038630   | Abnormal eating behavior                                    |                                 |
| OCTN1     | C 1672T      | Mushroom intolerance Crohn’s disease                        |                                 |
| NBPF3     | rs4654748    | Vitamin B6 deficiency                                       | Low vitamin B6 levels           |
| TF        | rs3811647    | Low iron levels anemia                                      | Increased iron concentrations   |
| SLC23A1   | rs33972313   | Vitamin C deficiency                                        | Low levels of vitamin C         |
| BCDIN3D   | rs7138803    | Diabetes                                                    |                                 |
| CB1-R     | rs1049553    | Renal fibrosis Metabolic disorders                          |                                 |
| GNPDA2    | rs1093897    | Obesity risk                                                |                                 |
| FGF21     | rs838153     | Metabolic disorders Diabetes                                | Increased carbohydrate intake Decreased fat intake |
| KCTD15    | rs29941      | Diabetes                                                    | Higher carbohydrate intake      |
| NECR1     | rs2815752    | Diabetes                                                    | Higher carbohydrate intake      |
| TEMEM18   | rs6548238    | Obesity                                                     |                                 |
| MAP2K5    | rs2241423    | Diabetes                                                    |                                 |
| QPCTL     | rs2287919    | Diabetes                                                    |                                 |
| TNN15K    | rs1514175    | Diabetes                                                    |                                 |
| GSK3B     | rs534555     | Bipolar disorder Brain disorders                            | Response to antidepressant pharmacotherapy |
|           | rs11925868   |                                                             |                                 |
|           | rs11927974   |                                                             |                                 |
| FKBPS     | rs1360780    | Depression Post-traumatic stress disorder                   | Glucocorticoid receptor sensitivity |
| OXTR      | rs53576      | Post-traumatic stress disorder                               | Regulation of mood, anxiety and social biology |
| AKT1      | rs2494732    | Psychosis                                                   | Regulation of dopamine levels in the prefrontal cortex |
| ANK3      | rs10994336   | Bipolar disorder                                            | Sodium channel activity increased excitatory signaling |
|           | rs1958526    |                                                             |                                 |
| CACNA1C    | rs1006737    | Mood instability Depressive and bipolar disorder            | Altered brainstem volume increased excitatory signaling |
| CHRNA5    | Asp598Asn    | Cigarettes smoking                                          | Neurotransmission               |
| CHRNA5    | rs1696968    | Pleasure response from smoking                               | Neurotransmission               |
| OPRM1     | Asn40Asp     | Addictive behavior                                          |                                 |
| CNR1      | rs2023259    | Addictive behavior                                          | Normal reward signaling         |
| FAAH      | C 385A       | Addictive behavior                                          | Difficulty with withdrawal       |
| GABRA2    | rs279858     | Sedation Amnesia Ataxia Anxiety Insomnia Alcohol addiction  | Improved GABA production        |
ening the person’s susceptibility to nutrition-induced obesity [3]. The major genetic variants influencing metabolic pathways involved in the increased risk of obesity and obesity-related disorders are located in the following genes: ADIPOQ, FTO, LEPR, LEP, MC4R, INSRG2, PPARG, PCSK1, ADBR3, ADBR2, PPARG, APOA1, GHR, APOA5, FABP2, LIPC, MTNR1B, TCF7L2, CETP, GIPR, NPY, IRS1, and PCSK1 (Tab. I) [2, 56, 57]. Candidate genes involved in the regulation of food intake, lipid metabolism, or release of intestinal hormones have been investigated. For example, the FABP2 (fatty-acid-binding protein 2) gene, expressed in the epithelial cells of the small intestine, is involved in fat absorption. Genetic variants in this locus may cause higher fat absorption and obesity [58]. Similarly, the PPARG (peroxisome proliferator-activated receptor-gamma) gene is expressed in the fat cells and plays a major role in adipocyte differentiation. In their study, Deeb et al. [59] demonstrated an association of the PPARG gene with insulin sensitivity and body mass index. So far, almost 500 genetic loci have been identified in association with obesity traits, like waist-to-hip ratio or body mass index [60].

The FTO genetic locus that is associated with fat mass and obesity is considered to have the strongest effect upon body weight. The TMEM18 (transmembrane protein 18) gene is also known to regulate appetite, body weight, and obesity development. Similarly, decreased expression of the MC4R (melanocortin-4 receptor) gene results in a monogenic form of obesity [41, 47, 61, 62].

| Gene       | Polymorphism | Putative disease risks                  | Effect                                      |
|------------|--------------|-----------------------------------------|--------------------------------------------|
| 1A HTR1A   | C -1019G     | Depressive disorder Bipolar disorder    | Reduced serotonin signaling at post-synaptic sites |
| SLC6A4     | rs1042173    | Addiction-related disorders              | -                                          |

**Genetic polymorphism interaction with physical activity**

Research studies have revealed the significance of diet in combination with physical activity for maintaining a healthy body weight. Genetic polymorphisms associated with obesity might influence physical activity levels; conversely, physically active lifestyles might reduce obesity risk. For example, sixteen interventional and cross-sectional research studies performed on children and adults of European, East African, and African origin reported a significantly strong association of FTO intron 1 with physical activity [61, 62]. Additionally, a recent meta-analysis involving 111,421 individuals of European descent established a significant association between physical activity and genetic risk score for twelve obesity-linked polymorphisms [63, 64]. Similarly, another meta-analysis involving 19,268 children and 218,166 adults found higher leisure-time physical activity reduces FTO variants effects, whereas increased sedentary periods, like watching TV, enhance genetic predisposition to increased adiposity [65]. In the US, the Diabetes Prevention Program involving 869 individuals reported a strong association of FTO genetic variants with one-year lifestyle intervention processes related to physical activity, weight loss, and diet with reference to the subcutaneous fat area. They found an association of the minor allele of an FTO variant with more subcutaneous fat mass within the control group as compared to the lifestyle intervention group. Similarly, another recent study indicated that physical activity, along with a vegetarian diet, could reduce elevated body mass index due to the minor allele of a variant in the FTO gene (rs3751812). Other physical activity-related genes are influenced by dietary intake and are involved in muscle strength and structure [66-68].

Additional studies have described the protective effect of physical activity on obesity-linked genetic variants in the form of a combined genetic risk score. In their study, Li et al. [69] have shown that the genetic susceptibility to obesity in individuals with higher genetic risk scores could be reduced by high physical activity levels [29, 69].

**Conclusion**

Every human being possesses an exclusive nutritional blueprint inside his/her genes. Bioactive food components and nutrients affect the expression of such genes. Nutrigenomics is the branch of science that analyzes gene-nutrient interactions, allowing the development of personalized nutrition approaches to maintain good health and prevent disease. Nutrigenomics combines different branches of science like nutrition, bioinformatics, genomics, molecular biology, molecular medicine, and epidemiology. Studies have revealed a myriad of interconnections at various levels amongst nutrients and genes. More specifically, genes regulate the intake and metabolism of different nutrients, while nutrients positively or negatively influence the expression of different genes at the epigenetic, transcriptional, and translational level. Nutrigenetic testing may soon become a fundamental technique to plan individualized weight loss and to better understand gene-nutrient interactions.

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Conflicts of interest statement

Authors declare no conflict of interest.

Author’s contributions

MB: study conception, editing and critical revision of the manuscript; AKK, GB, KD, JK, KLH, LS, FF, SN, MP, PC, FB, PG: literature search, editing and critical revision of the manuscript. All authors have read and approved the final manuscript.

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