Review

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 translational 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 micronutrients [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 micronutrients – 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. Transcriptomics also helps the identification of genes, metabolites, or proteins that alter pre-disease states and assists 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 monoterpene 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* (methylenetetrahydrofolate 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 insaturated 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 *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 Neural tube defects	Folate degradation
MTHFR	rs1801133	Breast cancer Homocystinuria Cardiovascular diseases Diabetes Neural tube defects	Increased folic acid intake Macronutrient intake High levels of homocysteine Folate metabolism
	C677T		
	A1298C		
	A222V		
MTHFD1	R653Q	Neural tube defects	Higher folate intakes
MTR	rs1805087	Breast cancer	Lower folate concentration
	A2756G		
MTRR	A66G	Neural tube defects in offspring	Lower folate concentration
VDR	rs1544410	Osteoporosis Prostate cancer	Affects vitamin D levels
	T>C		
	rs11568820		
APOA1	rs670 rs5069	Metabolic syndrome	-
APOA2	rs5082	Cardiovascular diseases Obesity	Higher total energy, fat, and protein intake
APOA5	rs964184	Higher risk of early heart attacks Lipid metabolism disturbances Less weight gain on high fat diets	Greater reduction in TC and LDL-c Macronutrient intake
	rs662799		
APOB	rs512535	Metabolic syndrome	Low fat
APOC3	rs5128	Metabolic syndrome	Cholesterol metabolism
	C 3175G		
APOE	rs429358	Lipid metabolism disturbances	Macronutrient intake
	rs7412		
PNPLA3	rs739409	NAFLD	-
CYP1A1	TMsp1C	Breast and prostate cancer	Oxidative metabolism of estrogens
	Ile462Val		
CYP1A2	A>C	Heart diseases	Reduced ability to metabolize caffeine
CYP1B1	C194G	Congenital glaucoma	
CYP2R1	rs10741657 rs10766197	Lower vitamin D levels	Increased consumption of food rich in vitamin D Increased sun exposure
CYP17A	T34C	Congenital adrenal hyperplasia	Increased estrogen level
FTO	rs9939609	T2DM	Macronutrient intake
		Obesity	
FTO	rs8050136	Obesity	-
FTO	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
		Metabolic syndrome	
LCT	rs4988235	Obesity	-
PPARA	rs1800206	Lipid metabolism disturbances Hypercholesterolemia	Macronutrient intake Low n–6 fatty Acid
	rs6008259		

▶

Tab. I. *Continues.*

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 rs1800588l	Lipid metabolism disturbances	Higher decreases in TC and LDL-c 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	rs236918	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 C-889T	Chronic inflammatory diseases Periodontitis Coronary artery disease A few autoimmune diseases and cancers	Increased IL-1 plasma concentrations
IL-1B	C 3954T A -511G	Chronic inflammatory diseases Periodontitis Coronary artery disease A few autoimmune diseases and cancers	Increased IL-1 plasma concentrations
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 G -174C	Low-grade chronic inflammation Obesity Visceral fat deposition Insulin resistance Dyslipidemia Risk for cardiovascular diseases	Lower weight gains Tissue healing
IL6R	A>C	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 Gly258Ser	Lower vitamin B12 levels	Increased consumption of food rich in vitamin B12

Tab. I. *Continues.*

Gene	Polymorphism	Putative disease risks	Effect
ALPL	rs4654748	Lower Vitamin B6 blood concentration	Increased consumption of food rich in vitamin B6
CBS	rs121964962	Colorectal Cancer Homocystinuria Vitamin deficiency Dementia Heart disease Stroke	High RBC folate Removal of homocysteine
	rs1801181		
FOXO3	rs2802292	Longer lifespan	-
	rs2802288		
SIRT1	rs3740051	Higher basal energy expenditure	-
	rs2236319		
	rs2272773		
PEMT	rs12325817	Low choline	Increased choline intake
PLIN1	rs894160	Obesity	Macronutrients intake
GCKR	rs1260326	Lipid metabolism disturbances	Macronutrients intake
LIPG	rs4939833	Lipid metabolism disturbances	Macronutrients intake
LPL	rs328	Lipid metabolism disturbances	Macronutrients intake
	C1595G		
CELSR2	rs12740374	Lipid metabolism disturbances	Macronutrients intake
eNOS	G>T	Oxidative Stress	-
NOS3	rs1799983	Lipid metabolism disturbances	Macronutrients intake
CETP	rs1800777	Lipid metabolism disturbances	Reduced HDL-C concentrations
	G 279A		
CLOCK	rs4580704	Coronary heart disease	-
	T3111C		
CRY1	rs2287161	Type 2 diabetes Metabolic syndrome	Insulin resistance Low carbohydrate intake
T1R1	rs34160967	Dental caries	-
	rs41278020		
T1R2	rs35874116	Obesity Dental caries	High sensitivity to sweet taste
	rs9701796		
T1R3	rs307355	Dental caries	Reduced promoter activity
	rs35744813		
	rs307377		
T2R16	rs846664	Association with the aging process	Alcohol dependence
	rs978739		
TAS2R38	rs713598	Metabolic diseases Coronary heart disease	Bitter taste of PTC or PROP perception
	rs1726866		
	rs10246939		
SCNN1A	rs239345	Risk of hypertension Cardiovascular disease	-
	rs11064153		
SCNN1B	rs3785368	Risk of hypertension	-
	rs239345		
SCNN1G	rs4401050	Risk of hypertension	-
TRPV1	rs4790522	Cardiovascular risk disease	-
	rs8065080	Risk of hypertension	

Tab. I. *Continues.*

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	-
	rs3211938	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
	rs13246513	Obesity Metabolic syndrome	-
	rs3211842	Obesity Metabolic syndrome	-
GNAT3	rs1194197	Metabolic syndrome	-
	rs11760281		
OR7D4	rs61729907		-
	rs5020278		
OR11H7P	rs1953558	Obesity Dental caries Diabetes Cardiovascular disease Hypertension Hyperlipidemia Cancer	-
OR6A2	rs72921001	Gestational choriocarcinoma	-
LEPR	rs3790433	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
	Val66Met		
KCNB1	rs6063399	Obesity	Lower BMI
KCNC2	rs7311660	Obesity	Lower BMI

Tab. I. *Continues.*

Gene	Polymorphism	Putative disease risks	Effect
TMPRSS6	rs1421312	Anemia Damage of immune function, work performance, and damage of adolescent's psychological behavior and mental development	Iron deficiency
	rs2111833		
TUB	rs2272382	Obesity	Higher consumption of mono- and disaccharides Higher glycemic load
	rs1528133		
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 Chronic obstructive pulmonary disease	Carbohydrate responsiveness
	Gln27Glu		
ADRB3	Trp64Arg	Coronary heart disease Weight gain Type 2 diabetes mellitus	-
PON1	s854549	Cardiovascular disease Atherosclerosis	Detoxification/Oxidative stress Lipid levels
	r s854552		
	r s854571		
	rs854572		
Cdx-2	G3731A	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 overload	Iron metabolism
ADH1B	47His	Alcohol dependence	Systemic ethanol clearance
	369Arg		
	rs1229984		
ADH1C	349Ile		-
ALDH2	E487K	Alcohol metabolism	Acetaldehyde accumulation Alcohol metabolism
	rs671		
FADS1	rs174537	Abnormal lipid profile	PUFA metabolism
	rs174546		
AGT	T>C	Hypertension Cardiorespiratory disorders	Salt sensitivity Increased blood flow and respiration
	M235T		
MCM6	C 13910T	Lactose intolerance	-
HLA	DQ2/DQ8	Celiac disease	Gluten intolerance
BCO1	Ala379Val	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
	C-28T		
TNF-A	G -308A	Obesity Insulin resistance Dyslipidemia.	Whole body glucose homeostasis alteration

Tab. I. *Continues.*

Gene	Polymorphism	Putative disease risks	Effect
CRP	rs1205 G>A	Mental health disorder Depressive disorder Low-grade chronic inflammation	Higher levels of CRP
SULT1A1	G638A	Post-menopausal breast cancer	Estrogen load reduction
NQ01	C609T	Cancer	Protect from oxidative stress
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 Anterior cruciate ligament rupture Tennis elbow	Increase in content of type V collagen Decrease in fibril diameter and biomechanical properties of tendons
GPX1	C>T	Premature aging Prostate cancer	Protect against oxidative stress
GPX4	rs713041	Colorectal cancer	Lymphocyte GPx activities
CAT	C -262T	Premature aging	Protect against oxidative stress
EPHX1	rs1051740	Cellular damage Accelerated aging	Process toxins and pollutants
BDKRB2	C>T	Osteoarthritis Anxiety disorders Essential hypertension	Increased blood flow and respiration
VEGF	C>G	Neovascular eye disease Age-related macular degeneration	Increased blood flow and respiration
TRHR	rs7832552 rs16892496	Non-goitrous congenital hypothyroidism	Increased lean body mass
ACTN3	R577X	Alpha-actinin 3 deficiency	-
FABP2	Ala54Thr	Metabolic disorders	Fat absorption and metabolism
ADIPOQ	G -11391A	Chronic kidney disease Chronic obstructive pulmonary disease Metabolic disease	-
DRD1	rs4532 G-94A	Addictive behavior	Regulate neuronal growth and development Mediate some behavioral responses
DRD2	rs1800497 Taq1A/2A	Compulsive and risk-seeking behaviors Increased risk for co-morbid substance use disorders (alcoholism & opioids) Binge eating behavior Addictive disorder	Carbohydrate responsiveness Reduced carbohydrate intake
DRD3	Ser9Gly	Addictive behavior	Cognitive, emotional, and endocrine functions
DRD4	C521T	ADHD Opioid dependence Novelty seeking	-
ADBR3	Trp64Arg	Obesity and bodyweight-related disorders	Exercise responsiveness
GDF-8	K153R	Skeletal muscle-related disorders	-
SEP15	rs5859	Lung cancer	-
SEPP1	rs7579	Inflammation Cancer	Selenium availability and metabolism

Tab. I. *Continues.*

Gene	Polymorphism	Putative disease risks	Effect
BCMO1	rs1293492	Vitamin A deficiency	Low vitamin A levels
	rs7501331		
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	rs1049353	Renal fibrosis Metabolic disorders	-
GNPDA2	rs10938397	Obesity risk	-
FGF21	rs838133	Metabolic disorders Diabetes	Increased carbohydrate intake Decreased fat intake
KCTD15	rs29941	Diabetes	Higher carbohydrate intake
NEGR1	rs2815752	Diabetes	Higher carbohydrate intake
TMEM18	rs6548238	Obesity	-
MAP2K5	rs2241423	Diabetes	-
QPCTL	rs2287019	Diabetes	-
TNNI3K	rs1514175	Diabetes	-
GSK3B	rs334555	Bipolar disorder Brain disorders	Response to antidepressant pharmacotherapy
	rs11925868		
	rs11927974		
FKBP5	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
	rs1938526		
CACNA1C	rs1006737	Mood instability Depressive and bipolar disorder	Altered brainstem volume Increased excitatory signaling
CHRNA3	Asp398Asn	Cigarettes smoking	Neurotransmission
CHRNA5	rs16969968	Pleasure response from smoking	Neurotransmission
OPRM1	Asn40Asp	Addictive behavior	-
CNR1	rs2023239	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

Tab. I. *Continues.*

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	-

encing 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, INSIG2, PPARG, PCSK1, ADBR3, ADBR2, PPARγ, APOA1, GHRL, 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].

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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