Cominetti et al. Nutrire (2017) 42:10
DOI 10.1186/s41110-017-0033-2

Nutrire

POSITION STATEMENT Open Access

Brazilian Society for Food and Nutrition position statement: nutrigenetic tests

Cristiane Cominetti[1], Maria Aderuza Horst[1] and Marcelo Macedo Rogero[2*]

Abstract

Position statement: The Brazilian Society for Food and Nutrition (SBAN) bases the following position statement on a critical analysis of the literature on nutritional genomics and nutrigenetic tests: (1) Nutrigenetic tests are predictive and not diagnostic, should not replace other evaluations required to treatment, and should only be used as an additional tool to nutritional prescription; (2) Nutritionists/registered dietitians and other health professionals must be able to interpret the nutrigenetic tests and properly guide their patients, as well as build their professional practice on general ethical principles and those established by regulatory authorities; (3) It is extremely important to highlight that the misinterpretation of nutrigenetic tests can cause psychological and health problems to the patient; (4) Currently, there is insufficient scientific evidence for the recommendation of dietary planning and nutritional supplementation based only on nutrigenetic tests. This position statement has been externally reviewed and approved by the board of SBAN and has not gone through the journal's standard peer review process.

Keywords: Genetic polymorphisms, Epigenomics, Molecular biology, Nutrigenomics, Nutritional genomics

Background

Nutritional genomics bases

The Human Genome Project (HGP), formally launched in 1990 and finished in 2003, triggered a relevant foundation for research in the health field [1]. One of the sciences strongly influenced by this project was nutrition, through the consolidation of nutritional genomics. In the last years, a shift of paradigm in nutrition—represented by a change of focus on deficiency diseases to those with metabolic clinical manifestations, such as obesity, type 2 diabetes, and cardiovascular disease (CVD)—has benefited from studies evaluating the actions of nutrients and other dietary substances at a molecular level.

Nutritional genomics is a comprehensive term that covers nutrigenomics, nutrigenetics, and nutritional epigenomics, which refer to the way the environment, nutrients, and genes interact and how they influence phenotype, including the disease risks. Despite the specific boundaries of the three subdivisions, the term Nutrigenomics is often used as a synonym for Nutritional Genomics [2].

The basic concepts of nutritional genomics can be summarized as [3]:

1. Nutrients and food components act on the human genome, either directly or indirectly, to alter the expression or structure of genes;
2. Under certain circumstances and in some individuals, diet can be a serious risk factor of many diseases;
3. Some diet-regulated genes are likely to play a role in the onset, incidence, progression, and/or severity of noncommunicable chronic diseases (NCD);
4. The degree to which diet influences the balance between health and disease states may depend on the individual's genetic makeup; and
5. Dietary intervention, based on knowledge of nutritional requirement, nutritional status, and genotype (i.e., "individualized nutrition") can be used to prevent, mitigate, or even to cure NCD.

Nutrigenetic bases

Nutrigenetics studies the influence of genetic variability among individuals on nutritional needs, health status,

* Correspondence: mmrogero@usp.br
[2]Department of Nutrition, Nutritional Genomics and Inflammation Laboratory, Faculty of Public Health, University of São Paulo, Av. Dr Arnaldo, 715, CEP 01246-904 São Paulo, SP, Brazil
Full list of author information is available at the end of the article

and the risk of developing diseases [2]. The main objective of nutrigenetics is to study the effects of DNA variations, including single nucleotide polymorphisms (SNPs), copy number variations (CNV), and insertion and deletion (INDEL) polymorphisms in biological responses to the intake of energy, micronutrients, macronutrients, and dietary bioactive compounds [4].

SNPs are the most common type of variation in the human genome (about 90% of all variations) and refer to the replacement of only one nucleotide in a certain DNA position (Fig. 1) [2]. When the nucleotide exchange occurs in the coding region, it might promote a change in the structure and/or function of the translated protein. Due to the genetic code degeneracy, when the exchange of nucleotide does not alter the amino acid, the SNP is known as "synonymous" or "silent" because it does not change the translated protein (e.g., GUC → GU**A**, both encode a valine). When the change gives rise to a codon resulting in the translation of a different amino acid, the SNP is known as "non-synonymous" or "missense" (e.g., UUA → U**C**A, the first encodes a leucine and the second, a serine). If the nucleotide exchange results in a premature stop codon, the SNP will be known as "nonsense" (e.g., UAU → UA**G**, wherein the first encodes tyrosine and the second is a stop codon).

However, a polymorphism can occur all along the DNA molecule, including the gene promoter regions, which can exert influence (up- or downregulation) on gene expression. SNPs may also occur in introns and can interfere with protein synthesis by modifying the alternative splicing process [2, 5, 6]. Furthermore, the biological impact also depends on the homozygous or heterozygous condition, as the presence of only one risk allele is often enough to determine effects of protection or increased risk. It is important to highlight that the risk allele may be the minor (variant) or the major (wild), depending on the SNP studied.

An SNP may be identified in different ways. Firstly, most SNPs are cataloged in a public database (http://www.ncbi.nlm.nih.gov/snp/) under a registration number ("rs"—for example rs6756629). Another way to identify an SNP is through the nucleotide exchanged and the DNA position (for example, rs1050450 refers to a C to T change at position 593 of *GPX1*, thus 593C>T). When an SNP occurs in the gene promoter region, it is identified with a minus sign in front of the exchange (e.g., −74 G>A or 74 −G/A). Moreover, as polymorphisms in exons may alter the sequence of encoded amino acids, this alteration can also be used to identify these SNPs. For example, an SNP in the gene encoding the catechol-O-methyltransferase (*COMT*) is cataloged under the rs4680 and refers to a nucleotide exchange (G to A) at position 472. This exchange results in the codification of a methionine instead of a valine at the codon 158. Thus, the polymorphism may be named rs4680 or G472A (472G>A) or Val158Met. When an SNP occurs in the promoter region or in an intron, only the nucleotide exchange at a certain position of the DNA will be referred to. For example, the rs6721961 refers to the SNP −617 C>A in the promoter region of *NFE2L2* (gene that codifies the Nrf2, an antioxidant transcription factor). The rs894160 is the registration number of a polymorphism that occurs in an intron located in the perilipin gene and can also be named as 11482 G>A.

In 2012, the results of the 1000 Genomes Project showed that the human genome has about 38 million SNPs possibilities. Therefore, as the human genotype presents one variation at every 100–300 nucleotides, it

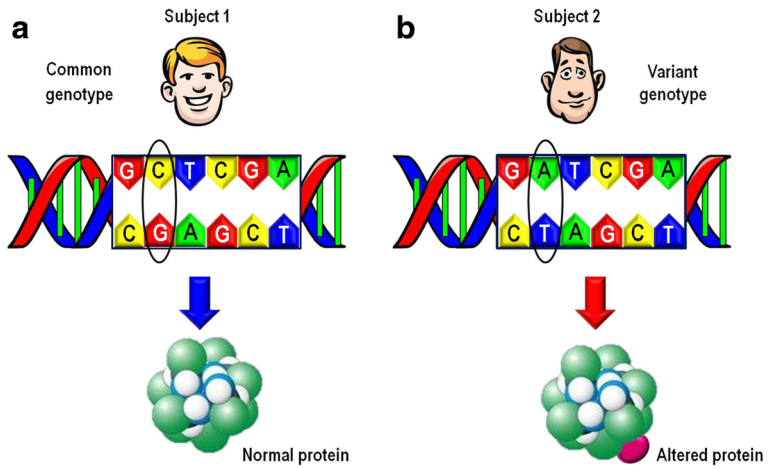

Fig. 1 Single nucleotide polymorphism: variations in nucleotides can occur all along the DNA sequence. Here, two examples of genotypes are illustrated: **a** in the "*common genotype*" there is a codon GCT, which is transcribed into CGA in mRNA and encodes an arginine. **b** In the "*variant genotype,*" nucleotide C was exchanged for an A. Codon GAT will be transcribed into CUA in mRNA, which encodes a leucine, promoting, therefore, a change in the translated protein. Adapted from Camp, Trujillo [2]

was estimated that one individual can display a subset of up to three million SNPs. In 2015, the 1000 Genomes project was finished, and more than 88 million variants were characterized, of which 84.7 million were represented by SNPs and 3.6 million, by insertion/deletion polymorphisms (INDELs) [7, 8]. It is important, however, to distinguish which SNPs have real importance in the nutrition context. For an SNP to be classified as of interest in nutrigenetic studies it must (I) be in genes that respond to diet and that are activated in chronic diseases, (II) be in genes encoding proteins considered key in metabolism, or in other DNA regions and that have hierarchical role in biological cascades, (III) have important functional consequences, (IV) be highly prevalent in the population of interest, and (V) be in genes with associated biomarkers [9].

A classic example that can be related to nutrigenetic is phenylketonuria (PKU), a rare autosomal recessive inborn metabolism error, caused by mutations in the phenylalanine hydroxylase gene (*PAH*). About 20 years after PKU discovery, it was found that the patients affected responded to dietary phenylalanine restriction [10]. This was, therefore, the first inborn metabolism error caused by changes in a single gene that responded to a nutrigenetic intervention [11]. However, considering that everyone who carries mutations in *PHA* will manifest some degree of PKU phenotype, this condition is considered monogenic and of high penetrance. On the other hand, NCD, such as obesity, type 2 diabetes, CVD, hypertension, and cancer, unlike PKU, are determined by the interaction of multiple genes, frequent genetic variations, and the disease phenotype depends on the environmental and behavioral factors (low penetrance).

In this context, some well-established polymorphisms importantly associated to NCDs or to related risk factors can be highlighted, such as rs9939609 (T>A) in intron 1 of fat mass and obesity-associated gene *(FTO)*, Ala222-Val (rs1801133 or C677T) in the methylenetetrahydrofolate reductase gene (*MTHFR*), and rs429358 + rs7412 in apolipoprotein E gene (*APOE*).

Frayling and coworkers (2007) analyzed 490,032 SNPs of 1924 British subjects with type 2 diabetes and 2938 controls in the searching for genetic variations related to this disease. Polymorphisms in *FTO,* mainly rs9939609, were strongly associated with the presence of type 2 diabetes, and this association was replicated in 3757 other patients with diabetes and 5346 controls [12].

Interestingly, risk alleles for type 2 diabetes were strongly associated with increased body mass index (BMI), suggesting that the relationship of polymorphisms with diabetes is mediated by changes in this anthropometric marker. The association of SNP *FTO* rs9939609 with changes in BMI and with the risk of overweight and obesity was estimated in 14,424 European adults and 10,172 children. In adults, A allele was positively correlated with an increased risk of overweight and obesity in individuals of all age groups and both sexes [12].

Afterwards, it was observed that mixed European descent men carrying the genotype associated with increased risk of obesity (AA) showed lower decrease of postprandial plasma ghrelin levels and of hunger feeling, compared to individuals carrying TT genotype [13]. In children, it was confirmed that A allele was associated with reduced satiety [14] and hyperphagia even after a meal [15]. In British children, SNP *FTO* rs9939609 was associated with eating behavior; those carrying the risk allele had early obesity because of excessive food intake, probably due to lower responsiveness to internal satiety signals and not to reduced energy expenditure [16].

The importance of MTHFR is related to its action on the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, for subsequent donation of a methyl group to homocysteine, so that it can be regenerated during the methionine/homocysteine pathway [17]. The largely studied polymorphism in *MTHFR* is Ala222-Val or 677C>T (rs1801133) [18, 19], which results in the synthesis of a more thermolabile enzyme with lower activity (about 30% lower in heterozygous individuals and 65% lower in homozygotes for the T allele). This SNP has been related to reduce plasma folic acid levels and high homocysteine levels [20], which may interfere with the global DNA methylation pattern, and increase the CVD risk. Regarding CVD, a meta-analysis of over 70 case–control studies (n = 16,849) showed that individual homozygotes for T allele had a 21% higher chance of developing ischemic acute myocardial infarction [21]. In this context, T allele carriers with hyperhomocisteinemia can benefit from higher intake of folic acid from food. There are, however, many other genes associated with blood homocysteine levels and DNA and histones methylation pattern [22].

Regarding cardiovascular risk, there is great emphasis on the role of apolipoproteins, mainly apolipoprotein E (APOE), which plays an important role in lipid metabolism, as it favors the uptake of triacylglycerol-containing lipoprotein, participates in reverse cholesterol transport and can influence CVD development [23]. It is estimated that 60% of the differences observed in serum cholesterol levels between different individuals are related to genetic determinants, including SNPs in genes of enzymes, transporters, and apolipoproteins. It is important to highlight that 14% of those differences are defined by the SNPs *APOE* rs429358 and rs7412 [24, 25]. The SNPs *APOE* rs429358 + rs7412 results from two variations in exon 4 of the gene, which cause changes that are differentiated by the cysteine and arginine content at codons 112 and 158, respectively. These changes result in three

major alleles: ε2 (cysteine in both positions), ε3 (cysteine at position 112 and arginine at 158), and ε4 (arginine at both positions). These alleles give rise to six possibilities of genotypes: E2/E2; E3/E3; E4/E4; E2/E3; E2/E4; and E3/E4 [24].

Meta-analysis of 82 studies related to lipid profile of healthy individuals and 121 studies of individuals with CVD showed significant relationship between *APOE* genotypes, serum levels of cholesterol in low-density lipoprotein (LDL-C), and the risk of developing CVD. The results showed that because ε4 allele carriers present higher levels of serum total cholesterol and LDL-C, they are more likely to develop CVD compared to carriers of other alleles [25]. In a study with Brazilian individuals, it was found that the risk of dyslipidemia was three times greater in subjects carrying ε4 allele when compared to ε2 carriers [26]. However, ε2 allele appears to be associated with higher plasma triacylglycerol levels [27].

Although certain genotype variations can potentially increase the risk of diseases, diet can influence gene expression patterns and act to reduce the risk or as therapy, with consequent possibility of earlier positive results.

Nutrigenomics bases

Nutrigenomics refers to the study of gene expression modulation by nutrients and food components. In this regard, specific nutrients or food components may increase or decrease the expression of a given gene. Gene expression regulation, in the context of nutrigenomics, can occur through direct and indirect mechanisms. Direct mechanisms are mediated by low molecular weight, carrier-mediated, and lipid-soluble molecules. In contrast, indirect mechanisms are mediated by larger and hydrophilic molecules that interact on the cell surface [28].

The action of calcitriol, the vitamin D active form, represents an example of a direct nutrigenomic mechanism in which this molecule acts as a ligand for the nuclear receptor, the vitamin D receptor (VDR). Binding to this nuclear receptor causes vitamin D to associate with another protein, retinoid X receptor (RXR), which results in the formation of RXR-VDR heterodimer. In turn, this complex interacts with specific nucleotide sequences in the DNA, called vitamin D response element (VDRE). VDRE activation allows other transcription factors to bind to this complex, which then modulates transcriptional activity of target genes [29, 30] (Fig. 2).

Experimental studies have shown, for example, that vitamin D modulates inflammatory responses in macrophages, which are cells with a large capacity for cytokine production, particularly tumor necrosis factor (TNF)-α, one of the most important inflammatory products released from these cells [31]. The TNF-α gene promoter region contains a complex array of potential regulatory elements. Transcriptional activation of the TNF-α gene in macrophages has been demonstrated to be predominantly dependent on the nuclear factor-kappa B (NF-κB), which has four binding sites in the TNF-α promoter, and is a major regulator of gene transcription involved in immune, inflammatory, and stress responses. Except for mature B cells, in which NF-κB is constitutively nuclear, in all other cell types (including macrophages), NF-κB is maintained in the cytoplasm via an association with the inhibitor of kappa B (IκB), which masks NF-kB nuclear localization sequence [32]. When cells are activated by proinflammatory cytokines [33], oxidants [34], or lipopolysaccharides (LPS) [35], the IκBs are rapidly phosphorylated at two serines within their amino-terminal regulatory domains. Phosphorylation of these two sites triggers polyubiquitination and subsequent degradation of IκBs. The loss of IκB in the cytoplasm and the appearance of NF-κB in the nucleus occur simultaneously. Activated NF-κB then binds to cognate DNA binding sites and induces gene transcription [36].

In macrophages incubated with $1,25(OH)_2D3$ and then stimulated with LPS, vitamin D seems to upregulate IκB-α levels by increasing messenger RNA (mRNA) stability and decreasing IkB-α phosphorylation. The increase in IκB-α levels leads to a reduction in nuclear translocation of NF-κB, thereby causing a decline in this nuclear factor activity. Due to the key role of NF-κB in pro-inflammatory response modulation, it may be suggested that 1,25(OH)2D3 plays an anti-inflammatory action in macrophages [37].

Regarding indirect mechanisms that control gene expression, nutrients or food components activate signaling pathways, which in turn promote the translocation of specific transcription factors from the cytoplasm to the cell nucleus. Transcription factor binds to the promoter region of specific genes inducing gene transcription. Curcumin, a yellow pigment found in the rhizome of *Curcuma longa* and known as turmeric, represents an example of a food component that induces an indirect mechanism of gene expression regulation (Fig. 3) [38]. Several studies have characterized the anti-inflammatory actions of curcumin, combined with its antibacterial, antiviral, antifungal, and antitumoral effects (reviewed in ref. [39]). Curcumin modulates several in vitro molecular targets, including the NF-kB, and the expression of genes induced by this transcription factor, such as those encoding cyclooxygenase (COX)-2, inducible nitric oxide synthase (iNOS), vascular cell adhesion molecule 1 (VCAM-1), intracellular adhesion molecule 1 (ICAM-1), TNF-α, interleukin (IL)-1, IL-6, IL-8, IL-12, and interferon gamma (IFN-γ). In addition, this molecule also inhibits the production of TNF-α induced by phorbol-12-myristate-13-acetate (PMA) and hydrogen peroxide. Thus, it has been suggested that the anti-inflammatory

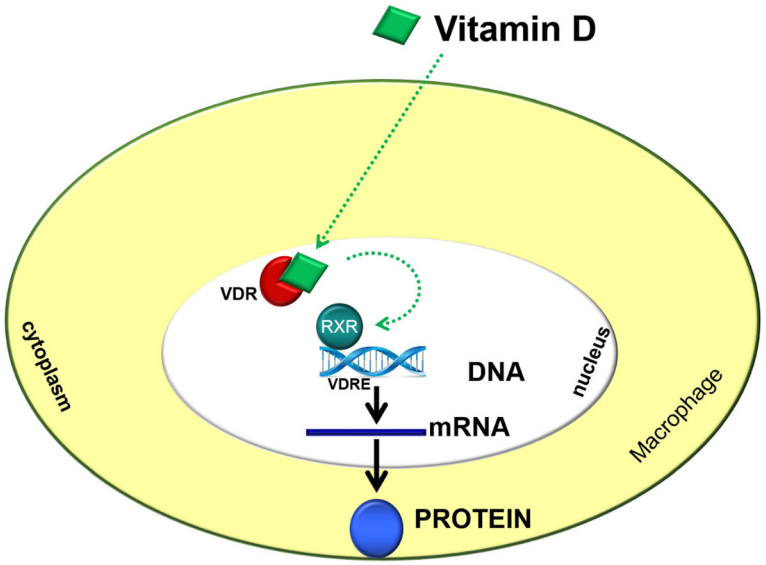

Fig. 2 Example of a direct nutrigenomic mechanism mediated by calcitriol. Modified from Nagpal et al. [30]. *VDR* vitamin D receptor, *RXR* retinoid X receptor, *VDRE* vitamin D response element

effects of curcumin may be attributed, in part, to its ability to trap reactive oxygen species radicals [40, 41].

In summary, nutrigenetics and nutrigenomics studies, with distinct approaches to investigate the interaction between diet and genes but with the common goal of optimizing health through personalized diet, provide effective approaches to understand the complex relationships among nutrients, food components, genetic variants, and the biological system [42]. It is important to highlight that feeding modulates several genomic networks with different molecular targets, which makes research in this area challenging due to the need for high-performance molecular biology tools.

Nutritional epigenomic bases

From a simple and comprehensive way, epigenetic can be described as reversible changes in gene expression profiling, without alteration of the DNA sequence and that are inherited even in the absence of the initiation signal or event. The genome epigenetic profile is

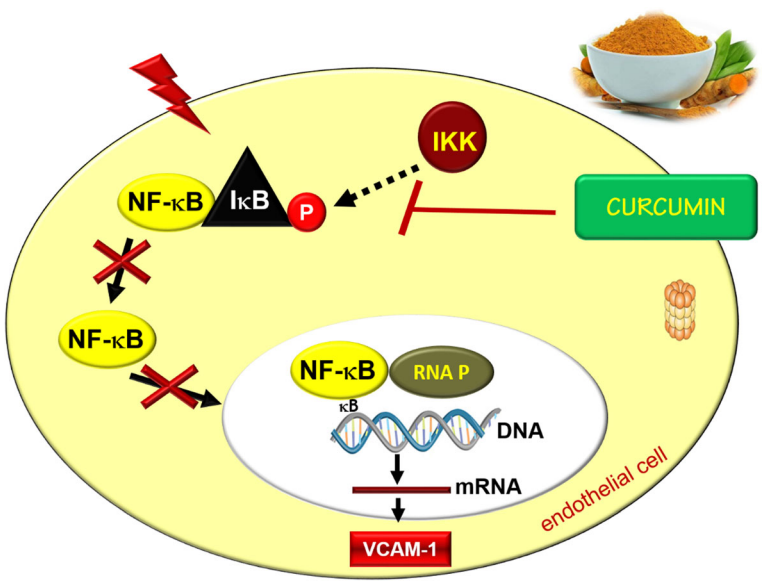

Fig. 3 Example of an indirect mechanism mediated by curcumin. Adapted from Aggarwal [38]. *NF-kB* nuclear factor-kappa B, *IkB* kappa B inhibitor, *IKK* IkB kinase, *P* phosphorylation, *RNA P* RNA polymerase, *kB* kB sites, *VCAM-1* vascular cell adhesion molecule 1

reversible, in contrast to the static DNA sequence, and dynamically varies from tissue to tissue and in accordance with environmental exposure, featuring a high degree of plasticity [43, 44]. Dietary patterns influence cellular metabolism by modulating epigenetic events. Accordingly, nutritional epigenomics studies the influence of the diet on epigenetic mechanisms that regulate activity and gene expression [2, 45].

The main known epigenetic events include DNA methylation, post transcriptional modification (acetylation, methylation, phosphorylation, etc.) in histone proteins, and noncoding RNA activity (mainly microRNAs). Similarly to genetic information, epigenetic marks are to be transmitted to the next generation in order to be qualified as true epigenetic information [43].

Many of those epigenetic marks, obtained at the embryonic stage, are closely related to the mechanisms of genomic imprinting and metabolic programming and are dynamically regulated by epigenetic remodeling throughout life. In humans and rat, the physiology of the fetus is influenced by the nutritional and emotional state of the mother (especially the stress level) [46, 47]. Nutrients and dietary bioactive compounds might modulate such events (Fig. 4) to promote or impair health, inducing silencing or transcriptional activation of specific genes, which ultimately alter the function and cellular metabolism [48].

Some nutrients that modulate epigenetic events include (but are not limited to) amino acids such as lysine (required for modifications on histone residues); methionine (precursor of S-adenosylmethionine (SAM—methyl donor); short chain fatty acids such as butyric acid; vitamins or similar essential compounds, especially vitamins B_2, B_6, B_{12}, and folic acid, choline and betaine; and minerals such as magnesium and zinc [49, 50]. Specific nutrients are needed to boost metabolic pathways that result in methylation and both scarcity and excess of these nutrients can directly affect the epigenome. Therefore, a high-fat diet can influence the DNA methylation status, for example [51]. However, the status of folic acid, vitamin B_{12}, methionine, choline, and betaine appear to be the most important factor for the DNA methylation pattern, especially because these nutrients play a critical role in methyl groups' availability and collectively regulate the one-carbon metabolism [52].

Dietary bioactive compounds are also able to modulate the DNA methylation pattern. In cancer cell cultures, apigenin and luteolin inhibited DNA methyltransferases activity (DNMTs), with consequent increase in apoptosis and decrease of cell proliferation. In turn, resveratrol seems to reduce methylation of *PTEN* promoter region, which reactivates the expression of this tumor suppressor gene in breast cancer cell culture [53].

Another interesting example is calorie restriction, which if not accompanied by nutritional deficiencies, appears to be related to longevity. This effect may be partly mediated by modulation of epigenetic events, as it

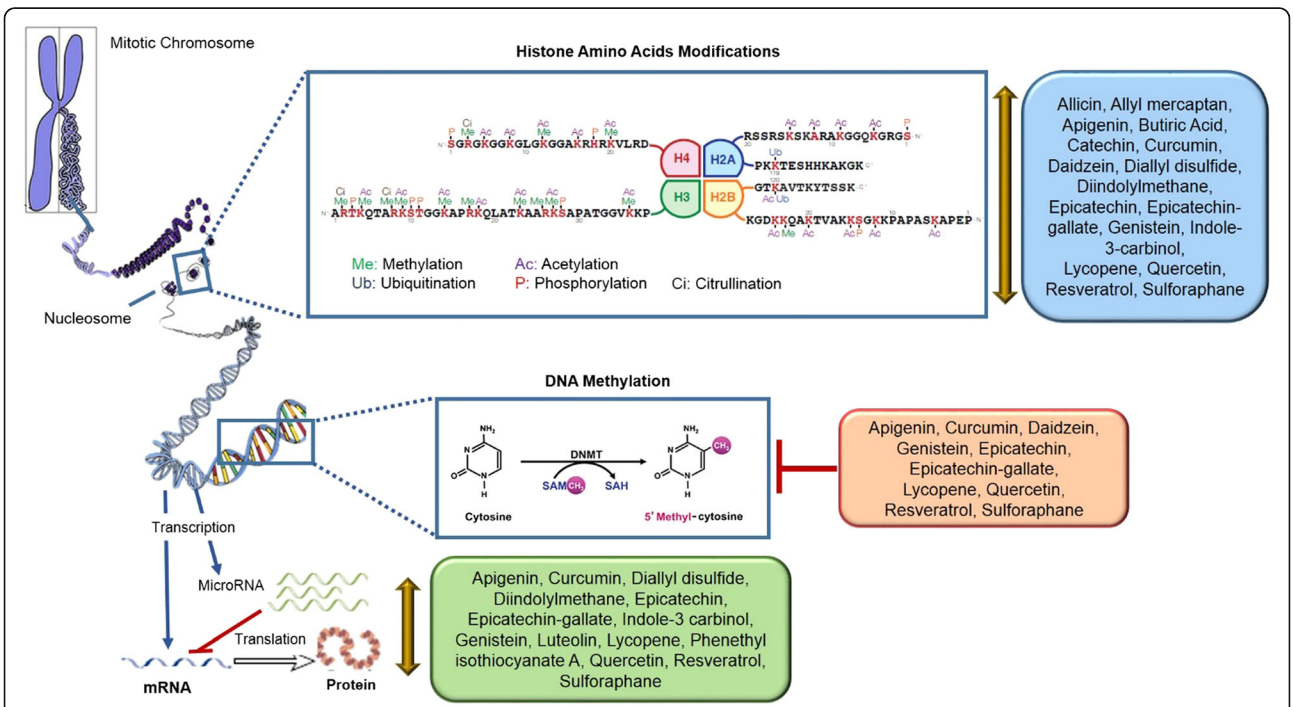

Fig. 4 Overview of epigenetic mechanisms regulating gene expression. Dietary phytochemicals involved in DNA methylation patterns, histone modifications, and changes in microRNA expression. Adapted from Shankar et al. [75]

causes activation of the histone deacetylase sirtuin 1 (SIRT1). SIRT1 also induces deacetylation of histone associated to the *FOXO1*, *FOXO3*, and *FOXO4* genes, which results in modulation of cell cycle, increased defenses against reactive oxygen species, and reduced apoptosis [54].

Evidence suggests that diet can affect the disease development risk also by modulation of miRNA expression [55], such as in the response to high-fat diet induced obesity in mice [56] and in the responses to adipogenic differentiation control in offspring of rats treated with different lipid sources [57].

Epigenetic events may be modulated according to the environment and provide further explanation on how diet can influence biological processes and determine phenotypes. Knowledge of such control mechanisms and the establishment of epigenetic biomarkers can help in the prescription of personalized diets for health promotion. However, one of the most intriguing questions is what would be the "ideal" epigenomic profile for an individual, as each cell type and even different cell types present distinct epigenetic patterns. Also, there is evidence that epigenetic modifications could be transgenerationally inherited and early-life-acquired epigenetic marks could be reverted throughout life via nutritional interventions [58]. But, further studies are necessary to the full understanding of these mechanisms.

Knowledge on nutritional genomics is being continuously expanded, and there is growing interest of companies in the development and commercialization of nutrigenetic tests. Health professionals can use these tests as an additional tool in health promotion.

Nutrigenetic tests

It is largely known that under the same nutritional intervention, individuals have different biological responses. Thus, nutritionists/registered dietitians have the opportunity of using additional tools to prescribe diets, such as those that identify some genetic characteristics. In this context, one of the most intriguing challenges in nutrition is deciding what dietary pattern better fits individual nutrient requirements, which are influenced by their genotypic profile.

Genetic tests for diagnosis purposes have been used in traditional medicine for several years to confirm a suspected diagnosis, in the screening of inherited diseases in individuals with familial history and in preimplantation diagnosis. Most of these tests evaluate autosomal diseases related to a single gene, in which mutations reflect high probability (100% chance) of disease development, such as in Huntington's disease [59].

Nutrigenetic tests, however, are classified as predictive genetic tests, which means they are used to assess genetic variations that increase or decrease the risk of an event but that under no circumstances can, singly, ensure a diagnosis. On the other hand, these tests can be used under the precision medicine approach or 4P genomics—personalized, predictive, preventive, and participatory [60]. Precision medicine is based on genomic biomarkers targeting specific therapeutic interventions for the individuals [61].

Nutritional genomics is an important part of precision medicine, and nutrigenetic tests are being marketed directly to the consumer (DTC). This approach is worrying because, oftentimes, the knowledge necessary to properly interpret the results is insufficient. The Food and Drug Administration describes some interesting recommendations on DTC genetic tests. The main one is that pre-symptomatic and highly predictive DTC tests available online should not be used without the involvement of a physician or a genetic specialist. However, the FDA and a group of experts concluded that nutrigenetic tests have a low-risk level if analytically and clinically validated [62].

In the UK, the first nutrigenetic test was launched in 2001, but scientists and clinicians were skeptical that researches were ready to be translated into clinical trials [63]. In Brazil, nutrigenetic tests emerged from 2011 and currently there is an increasing number of companies offering genotyping services with different approaches and diverse polymorphisms in the tests.

Therefore, with the increased opportunity of carrying out predictive nutrigenetic tests, it is crucial that nutritionists/registered dietitians and other health professionals are able to understand, interpret, and use these tests properly. It should be noted that the nutritional prescription based on nutrigenetic tests must focus on health and life quality promotion [64].

Nutrigenetic tests focus on the analysis of genetic variations, especially SNPs, that can predict the individual nutritional needs, in order to guide interventions to reduce the risk of chronic diseases. In the last years, the expression "one size does not fit all" has been applied in studies about genes—diet interactions. Thus, nutrigenetics can be a tool to achieve the optimum amounts of nutrients in an individual and personalized approach [65].

Nevertheless, it is necessary to point out that although the first draft of the human genome have been announced since 2001, the function of all genes and the possible relationships between genes and diseases are still unknown. Therefore, it should be emphasized that nutrigenetic tests, solely, are not sufficient for diet customization and not even for prescribing supplements. In this context, it is noteworthy that unlike monogenic

diseases (e.g., phenylketonuria), nutrigenetic tests for complex polygenic conditions (e.g., obesity, cancer, type 2 diabetes, intolerances, dyslipidemia, hypertension, etc.) are only predictive of the associated risk.

Nutrigenetic tests are based on the principle that individuals respond differently to acute or repeated exposure to a particular nutrient, a dietary bioactive compound, or to a combination of them. Usually, these tests analyze polymorphisms in genes primarily involved with obesity and associated comorbidities, metabolism and transport of nutrients, pro-inflammatory response, and detoxification enzymes and antioxidants. Therefore, according to the genetic variations of an individual and considering other aspects, such as family history, clinical evaluation, and biochemical tests, personalized nutritional counseling can be prepared and include nutritional and lifestyle advice to achieve specific goals, such as weight loss or blood glucose and cholesterol control.

It is also important to highlight that all the possible associations between SNPs and other factors that contribute to the emergence of diseases are not completely known, which implies that the absolute risks from such associations are still low. In addition, in polygenic conditions, beyond the influence of several SNPs, it is extremely important to consider the role of environmental factors, such as the level of physical activity, emotional stress, smoking, alcohol intake, and dietary habits, which can modify gene expression patterns (especially through epigenetic mechanisms) and the risk of developing diseases. In this context, epigenome-wide association studies (EWAS) help to identify epigenetic biomarkers of metabolic health, which will be useful for monitoring the individual who receives a nutritional prescription [66]. Another point to be considered is the interpretation of nutrigenetic tests results, as it depends on many factors including how many and which SNPs are evaluated, which studies supported the interpretation, environmental factors, and the interaction with other unassessed genetic factors.

One example of SNP evaluated in nutrigenetic test is rs4988235, lactose intolerance-associated. Lactase is encoded by the *LCT* gene, located in chromosome region 2q.21 and highly expressed in newborns. After the lactation period, *LCT* expression decreases and adults lose, at least in part, the ability to metabolize lactose. However, some individuals retain this ability, which is known as persistence of lactase, a dominant condition that arose in northern Europe from mutations in *MCM6* gene, adjacent to the *LCT* gene, in a region acting as a promoter of lactase expression. In Europeans, the polymorphism associated with lactase persistence is *MCM6* –13910 C>T (rs4988235), wherein the presence of T allele determines the persistence of the enzyme. However, in African Americans and Asians, the frequency of this polymorphism is very low and cannot be related to lactase persistence, which highlights ethnic differences involved in the determination of specific phenotypes [67].

Another example of SNP evaluated in nutrigenetic tests is rs762551 (–164 A>C) in *CYP1A2*. This gene encodes CYP1A2, a xenobiotic metabolizing enzyme responsible for ~13% of hepatic cytochrome P450 activity [68] and, among other compounds, for caffeine (1,3,7-trimethylxanthine) metabolism [69]. The presence of C allele (also referred to as *CYP1A2* *1F) associates with reduced enzyme metabolizing capacity compared to the presence of two allele A (also designed as *CYP1A2* *1A/*1A). Therefore, individuals carrying two major alleles (AA) are classified as "fast" metabolizers, while those carrying minor alleles (one or two) are "slow" metabolizers of caffeine. The main clinical relevance of being fast or slow metabolizer of caffeine is related to the risk of cardiovascular disease. In this context, slow metabolizers of caffeine showed higher risk of acute myocardial infarction with increased coffee consumption (>500 mL/day), which was not observed in fast metabolizers [70].

In a clinical practice experience, Arkadianos and colleagues (2007) [71] evaluated 50 patients who underwent a nutrigenetic test and a group of 43 patients (matched for age, sex, and frequency of visits) who received a standard diet for weight loss. Custom guidelines were directed according to the genetic profile (24 SNPs) of each patient. In the first trimester, patients of both groups showed similar weight reduction. However, after 1 year of intervention, patients who received nutritional prescription according to the genetic profile continued to lose weight, while those who received the traditional prescription regained weight. Moreover, only the group who received the guidelines customized by genotype showed a significant improvement in fasting glucose levels.

Another study aimed to compare the results of standard nutritional versus genotype customized guidance. The diet was prescribed according to the results of seven SNPs [*APOA2* (rs5082), *ADIPOQ* (rs17300539), *FTO* (rs9939609), *KCTD10* (rs10850219), *LIPC* (rs1800588), *MMAB* (rs2241201), and *PPARG* (rs1801282)]. Nutritional counseling was standardized between groups, and the nutrigenetic test group followed a diet with different carbohydrates, lipid, and protein distribution (balanced, low-carbohydrate, low-fat, or Mediterranean diets). There was no significant difference between the groups in the percentage of participants who showed a reduction of 5% of their body weight after 8 or 24 weeks of intervention. Both groups had difficulty to follow the diets; however, adherence correlated with weight loss in the nutrigenetic test group, which did not occur in the control group [72].

Complex diseases such as type 2 diabetes, cancer, and cardiovascular disease are the result of interaction between environmental and genetic factors, and genetic variations are only predictors of risk. Because of the large number of possible interactions, the association between genes, diseases, and the environment is not yet fully understood, which excludes the possibility of diagnosis through nutrigenetic tests. Thus, nutritional care based on nutrigenetic tests must include all stages of the conventional nutritional care, with the investigation of family history, biochemical markers, nutritional and anthropometric aspects, risk factors of chronic diseases, and other features considered necessary by the health professional.

The decision to hold or not a nutrigenetic test should be taken by the patient. The health professional has the obligation of informing all the risks, benefits and limitations, and resolve doubts. The interpretation of the results should be careful, and the transmission of results to patients should be performed by trained professionals—preferably by a genetic specialist—who have sufficient knowledge of nutritional genomics, as such results can provide information about the risk of developing disease that has no cure, such as Alzheimer's disease. These results must be explained carefully to avoid alarming patients incorrectly. In this context, it is important to note that studies have revealed large gaps in knowledge and skills of health professionals, including nutritionists/registered dietitians, in developed countries such as Canada and the UK [73, 74].

Moreover, ethical issues must be widely discussed and considered. Aspects such as confidentiality of data; prediction of future health events; possible prejudice or discrimination arising from the results in any magnitude, including health insurances and employers; the population access to nutrigenetic tests; as well as aspects related to analytical quality of companies that provide these tests should be deeply evaluated. From a public health viewpoint, relevant social concerns relate to the possibility that genetic tests may cause social disparities. In addition, the need for specific legislations and inspection is paramount.

In short, nutrigenetic tests can help in the individualized nutrition prescription and should be used to complement the nutritional care and not replace any traditional assessment tool. Individual response to a nutrient intake is the result of interaction between metabolism; environment, social, spiritual, emotional and genetic aspects; and the microbiome. Therefore, nutrigenetic tests alone are not sufficient for diet customization, not even for prescribing supplements. However, there is overwhelming evidence for the use of certain genetic variations as a basis for nutritional prescription after a careful nutritional, anthropometric, clinical, and biochemical assessment.

The practical application of nutrigenetic tests also depends on the expansion of knowledge on the interactions between genes, nutrition, health, and disease and more specific information about the actual individual nutritional needs. In addition, more accurate information about the bioavailability of nutrients and dietary bioactive compounds are necessary, which will result in the reassessment of nutritional recommendations

Research on nutritional genomics has the potential to answer some important questions, for example, whether healthy phenotypes can be obtained from the adoption of some dietary patterns and if this outcome depends on the isolate intake of a specific nutrient or bioactive food component. In this context, it is very important to evaluate which are the specificities of nutrients and bioactive food components on different life stages.

Despite the obstacles faced by scientists, the nutritional genomics field undoubtedly continues to evolve and will impact the recommendation of nutrients and health promotion. SBAN, concerned with questions related to the use of nutrigenetic tests in the clinical practice of nutritionists and other health professionals, has put efforts in the elaboration of this technical position so that correct and updated information can be widely disseminated.

Summary of recommendations

- Nutrigenetic tests are predictive and not diagnostic, should not replace other evaluations required to treatment, and should only be used as an additional tool to nutritional prescription;
- Nutritionists/registered dietitians and other health professionals must be able to interpret the nutrigenetic tests and properly guide their patients, as well as build their professional practice on general ethical principles, and those established by regulatory authorities;
- It is extremely important to highlight that the misinterpretation of nutrigenetic tests can cause psychological and health problems to the patient;
- Currently, there is insufficient scientific evidence for the recommendation of dietary planning and nutritional supplementation based only on nutrigenetic tests.

Authors' contributions
CC, MAH, and MMR carried out the manuscript conception, manuscript drafting, and final revision of the study. All authors read and approved the final manuscript.

Competing interests
All authors of this article have roles in the Brazilian Society for Food and Nutrition: Cristiane Cominetti is a member of the Communication Committee and Courses Committee; Maria Aderuza Horst collaborates in the Communication Committee; and Marcelo Macedo Rogero is the second treasurer. Maria Aderuza Horst is a former consultant of Centro de Genomas®.

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Author details
[1]Nutritional Genomics Research Group, Faculty of Nutrition, Federal University of Goiás, Rua 227, sn, Quadra 68, Leste Universitário, CEP 74605-080 Goiânia, GO, Brazil. [2]Department of Nutrition, Nutritional Genomics and Inflammation Laboratory, Faculty of Public Health, University of São Paulo, Av. Dr Arnaldo, 715, CEP 01246-904 São Paulo, SP, Brazil.

Received: 23 February 2017 Accepted: 15 March 2017
Published online: 05 April 2017

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