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REVIEWS: CURRENT TOPICS

Nutritional genomics *era*: opportunities toward a genome-tailored nutritional *regimen*☆

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Abstract

There is increasing evidence indicating that nutritional genomics represents a promise to improve public health. This goal will be reached by highlighting the mechanisms through which diet can reduce the risk of monogenic and common polygenic diseases. Indeed, nutrition is a very relevant environmental factor involved in the development and progression of metabolic disorders, as well as other kind of diseases. The revolutionary changes in the field of genomics have led to the development and implementation of new technologies and molecular tools. These technologies have a useful application in the nutritional sciences, since they allow a more precise and accurate analysis of biochemical alterations, in addition to filling fundamental gaps in the knowledge of nutrient–genome interactions in both health and disease. Overall, these advances will open undiscovered ways in genome-customized diets for disease prevention and therapy. This review summarizes the recent knowledge concerning this novel nutritional approach, paying attention to the human genome variations, such as single-nucleotide polymorphisms and copy number variations, gene expression and innovative molecular tools to reveal them.
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1. Introduction

In the last decade, the human genome sequencing has allowed the identification of about 1000 mutations responsible for human diseases, and some disease-causing genes accounting for human multifactorial diseases, such as type 2 diabetes mellitus (T2DM), obesity, cardiovascular diseases (CVD) and cancer, have been unequivocally linked to the diseases [1–3].

Single-nucleotide polymorphisms (SNPs) in the human genome [4,5], potential sites for phenotypic variability, confer to individuals their uniqueness, due to the genome plasticity and to the genes–environment interaction [6,7]. Currently, although several SNPs in key genes have been associated with chronic metabolic disorders, a few association studies unambiguously confirm their involvement in the onset of these diseases [8,9]. An SNP, and a combination of them (haplotype), are not often responsible by themselves for disease phenotype, but they are likely to account for the genetic predisposition to develop the disease [10]. Indeed, although SNPs may cause some pathological conditions, the resulting phenotype is often influenced by environmental factors [11], which exert a selective pressure on the genomes and contribute to their evolution [12].

In the field of genetics, the term *environment* indicates all nongenetic contributions to variation for a phenotypic trait. The concept of "environment" includes all the factors possibly contributing to modify — ameliorating or worsening — a phenotype or acting as trigger for the initiation of a pathology. These factors can be briefly categorized in (1) exogenous and random (e.g., acute or chronic exposure to toxins, industrial chemicals, sunlight radiation, allergens, pollution, bacteria, etc.) and (2) endogenous and volitional (e.g., lifestyle, athletic training, caloric intake, alcohol and tobacco consumption, sedentary behavior, alteration of sleep cycle, etc.) [13]. Gene–environment interactions are considered as the different effects of the same environment on individuals with different genotypes or the differential phenotypic effects of environment on individuals with the same genotype [14].

For instance, it is known that common forms of overweight and obesity are likely to be polygenic, due to gene–gene and gene–environment. It has been suggested that "silent" gene variants are now contributing to the obesity epidemic through permissive interaction with an "obesogenic" environment, fuelled by energy dense and easily available foodstuffs [15].

Loos and Bouchard [16] hypothesized the presence of four categories of gene–environment interactions, possibly contributing to the severity of obesity. The first level is a monogenic form, affecting a few individuals whose obesity is not dependent on the exposure to a permissive environment. Conversely, another category consists of individuals that, despite a permissive environment, are genetically

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resistant to obesity. The remaining two levels of obesity comprise common or polygenic forms, including individuals with a strong or slight genetic susceptibility to develop the disease, but whose expression will depend on the exposure to "obesogenic" environment (i.e., diet). The canonical genome-centric approach usually fails to take into account a very relevant variable in the expression of genetic information and probably a major contributor to disease development, namely, the dietary components [1].

The interactions between the genetic background and the "obesogenic" environment are extremely dynamic, beginning at birth or even before and pursuing throughout the adulthood, and the food is an environment factor we are permanently exposed to, from conception to death. Therefore, diet represents a relevant environmental factor able to modulate gene expression during lifetime, although a long period of exposure to a "disease-predisposing" diet is necessary to develop the phenotype [17]. Indeed, a phenomenon known as metabolic imprinting or programming, referred to the embryo susceptibility to nutrient-induced adaptations in gene expression, has been described [18]. These metabolism-associated changes occur during embryonic development and can persist throughout the adulthood, predisposing to metabolic diseases [19].

Moreover, the relevance of the hormonal component should be considered as a major determinant in gene–diet interaction. This consideration is essential for the clinicians aimed to design a gene-based and age-/sex-specific dietary recommendation.

2. Nutrients, nutrition and genes

Nutrition is a very relevant environment factor that exerts its effect on the genetic background impairing or improving the likelihood to develop metabolic disorders [20]. From a public health perspective, the most practical translation of nutrition research consists in defining dietary recommendations to prevent the disease and to promote optimal health. To this purpose, dietary guidelines traced by the World Health Organization have been implemented to improve the health of individuals at high risk to develop pathological conditions (i.e., CVD, hypertension, obesity and diabetes).

In the era of the "*omics*," the nutrition science has introduced the terms *nutrigenomics* and *nutrigenetics*. To date, even though these terms are often used with the same meaning throughout the literature [21–25], the nutrigenetics and nutrigenomics should refer to different branches of the nutritional research. The nutrigenetics, also termed *personalized nutrition*, emphasize on the close "*cause–effect*" relationship between the nutritional regimen, which acts in different ways on the genetic background, and the development of a metabolic disorder [23]. The major goal of nutrigenetics includes the identification and characterization of genes, and nucleotide variants within these, that are associated with (or account for) the differential responses to nutrients. On the other hand, the nutrigenomics mainly focuses on the effect of nutrients, both *micro*- (vitamins and minerals) and *macro*nutrients (carbohydrates, fats and proteins), on the genome, proteome and metabolome.

The "*gene–nutrient interaction*" notion could be intended in different ways: (1) an SNP that regulates the effect of a dietary component on a specific phenotype, that is, obesity and plasma lipid concentrations; (2) a dietary component that modulates the effect of a genetic variant on a phenotypic trait; (3) dietary components that directly or indirectly act on DNA and gene expression at a molecular level.

Moreover, the nutrients directly or indirectly affect a disease phenotype by acting at different molecular levels. Indeed, dietary compounds may alter gene expression through modifications in the rate of transcription, affecting in turn the translation of such a protein, and may alter physiological posttranslational processes (Fig. 1). Taken together, these modifications — occurring at different cellular levels - may dramatically affect physiological processes such as metabolism, cell cycle/differentiation and inflammation, all of which are of great relevance in the disease onset.

2.1. Polymorphisms, haplotypes and nutrients

Although it has been postulated for decades that a genetic component acts in the differences to interindividual dietary response to a specific nutritional regimen [26], only in recent years, the effects of nutrition on human diseases have been demonstrated [23].

Nevertheless, past and also current dietary guidelines did not consider the dramatic differences in the individual response to variations in the nutrient intake, greatly affecting the efficacy of dietary recommendations. Moreover, the presence of SNPs within key genes has been shown to alter crucial pathways, affecting some physiological cellular activities and leading to increased susceptibility toward disease onset (see examples in Table 1). Indeed, several reported discrepancies in the response to disease outcome mainly derive from failing to account for the interindividual genetic differences.

For instance, inconsistencies in the response to dietary fiber intake have been explained on the rational basis of the presence of a common SNP, M235T, in the angiotensinogen gene. This nucleotide variation was shown to be directly linked to blood pressure variations after consumption of a dietary fiber [27]. The response to another very common dietary component, such as caffeine, may be strictly related to the presence of SNPs. Indeed, Rapuri et al. [28], during a study aimed to unravel the role of caffeine as a risk factor for bone loss in elderly women, found that women homozygous for *Taq*I SNP of the vitamin D receptor gene (*VDR*) with a caffeine intake greater than 300 mg/day had significantly higher rate of bone loss compared to control subjects [28,29]. It was also demonstrated that the caffeine dose-dependently decreases VDR protein expression and alkaline phosphatase enzyme activity in the osteoblasts. A reduced calcium absorption and retention was also shown in postmenopausal women, leading to a decrease in the bone mineral density (BMD) [30,31] and increased risk of hip fracture [32,33]. Two well-known *VDR* gene polymorphisms, *Bsm*I and *poly-A*, have been shown to affect the response to various dietary components leading to reduced BMD and osteoporosis. Moreover, they possibly represent a disease risk for their association with diet and colorectal cancer risk [34–36].

Other inconsistencies among clinical studies have been explained considering that dietary factors could modulate the effect of a genetic polymorphism. In this regard, some genetic variants in lipid-related genes have been studied for the past two decades, unfortunately resulting in a plethora of reports with different and controversial extents.

The gene encoding for apolipoprotein A-I, *APOA1*, is highly polymorphic, and a specific SNP in its promoter, 75G→A [39,40], has extensively been studied in association with high-density lipoprotein (HDL) cholesterol concentrations with conflicting results [41–43]. A study involving men and women fed with diets rich in saturated, monounsaturated or polyunsaturated fatty acids (PUFA) demonstrated that lower low-density lipoprotein (LDL) cholesterol levels were more marked in *A* allele carrier women than in homozygous for the *G* allele, but no effect was evident in men [44]. In another cohort of patients from the Framingham Offspring Study, a significant interaction in terms of HDL cholesterol concentration was observed between *APOA1* genotype and PUFA intake [45]. In women carrying the *A* allele, HDL cholesterol concentration significantly increased with increased PUFA intake. An opposite effect was observed in women homozygous for the *G* allele (HDL cholesterol concentration decreased as PUFA intake increased). These evidences

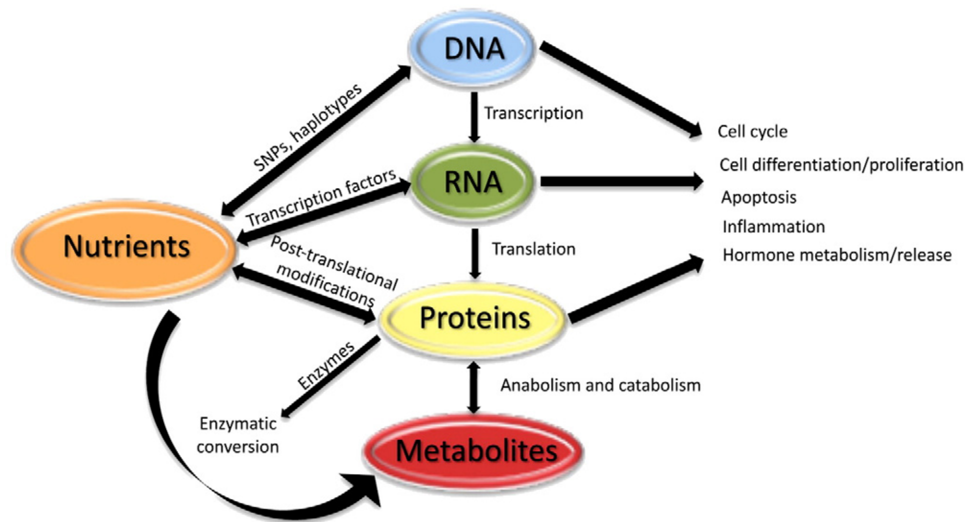

Fig. 1. Nutrients and their contribution to phenotype changes. Schematic representation of the molecular targets of dietary factors, and their contribution to establish such a phenotype. Nutrients may have direct and indirect interactions at different cellular levels. For instance, in the presence of SNPs in key metabolic enzymes, dietary compounds may be not completely metabolized or may detrimentally accumulate within the cells, or nutrients may directly affect gene transcription (hypo- or hypermethylation) and protein translation. An altered catabolism of nutrients, generating a variety of metabolites, may also give a contribution to the onset of disease phenotypes acting through global effects on several cellular processes, including cell differentiation/proliferation and inflammation.

show the possibility to provide tailored nutritional advices on the basis of genotype: women carrying the *A* allele should improve their PUFAs intake to increase HDL cholesterol hematic levels and to reduce the CVD risk, whereas *G/G* women should receive the opposite advice.

Moreover, the interaction between *Taq*IB polymorphism, within *CETP* gene, and alcohol consumption, in relation to plasma HDL concentrations, was also investigated [20]. The results have clearly shown that alcohol consumption can increase HDL concentrations in B1B1 individuals in a dose-dependent manner. Nucleotide variations within the apolipoprotein C3 (*APOC3*) — a primary determinant of the lipase-mediated catabolism and receptor-mediated clearance of triglycerides (TGs), rich lipoproteins — have been studied for their direct link to nutrition supplementation. Indeed, SNPs within the regulatory region of *APOC3*, such as −2854T>G, −482C>T and -455T>C, have been shown to reduce the expression levels, playing crucial roles in TG metabolism [46,47]. The absence, or the strong reduction of circulating ApoC3, a natural lipoprotein lipase (LPL) inhibitor, enhances fatty acid uptake from plasma TG in adipose tissue, leading to higher susceptibility to diet-induced obesity. Indeed, also an SNP within LPL-encoding gene, 1595 C>G, was associated with significantly lower TG levels (Table 1) [48].

Other crucial metabolic pathways such as antioxidant, detoxification and inflammation have been recently studied for their high susceptibility to the nutritional supplementation. In particular, oxidative damage, caused by reactive oxygen species (ROS) and other free radicals, is known to be involved in prostatic carcinogenesis. Dietary selenium (Se), a component of glutathione peroxidase in the manganese superoxide dismutase (MnSOD) antioxidant pathway, is indirectly linked to the antioxidant activity of this enzyme. Indeed, it has been shown that a particular SNP in the *SOD2* gene, Ala16Val, may alter MnSOD activity. Particularly, AA carriers have high levels of MnSOD expression, possibly leading to enzyme imbalance that, in turn, may induce toxicity if glutathione peroxidase activity is reduced due to low Se intake, or whether antioxidants are in high demand due to particular lifestyle factors, such as smoking [51]. Other examples of SNPs within *SOD3* and *NOS3* genes, with major effects on the antioxidant status, are reported in Table 1.

Consumption of vegetables and fresh fruit and the presence of SNPs in the detoxifying enzyme glutathione S-transferase M1 (*GSTM1*) and within other metabolism-related genes have been shown to modulate cancer risk (Table 1). In particular, strong inverse association was found between vegetable consumption and dietary intake of antioxidants and DNA adduct levels, only in *GSTM1*-null subjects [52], showing that a diet rich in antioxidants — to prevent or reduce DNA adduct formation — is useful only for subjects lacking the detoxifying activity of *GSTM1* isoenzyme (~50% of the general population). Similar effects have also been demonstrated for *GSTT1* and *GSTP1* null subjects (Table 1).

Inflammation is another crucial pathway greatly affected by the presence of nucleotide variations in key genes and by nutritional advices (Table 1). For instance, −308A SNP in the promoter of *TNFA* gene alters its expression levels, leading to high susceptibility to develop different types of cancer, such as stomach, invasive cervical cancer (ICC) and hepatocellular carcinoma (HCC) and also chronic and severe inflammatory diseases (Crohn and CVD). Single-nucleotide polymorphisms in the regulatory region of interleukin-6 (*IL-6*), a proinflammatory cytokine and major mediator of the acute phase response, influence transcription both in vitro and in vivo (Table 1). These variants have been associated with the increased risk of coronary heart disease. The effects of gene variations within both coding and regulatory regions of these genes can be modulated increasing dietary levels of n-3 PUFAs (omega-3 fats).

2.2. Effects of dietary components on gene expression

To date, it is widely accepted that most of the effects of the nutrition on human metabolic diseases and, in turn, on human health cannot be easily explained without a complete knowledge of the molecular mechanism underlying the nutrients' action [23]. In particular, the evidence shows that understanding how nutrition affects the metabolic homeostasis, influencing different cellular metabolic pathways, is a crucial event. Roughly investigating the role of gene–gene (epistasis) and gene–environment interactions will represent a reliable challenge for better elucidating the molecular basis of the multifactorial metabolic disorders [59,60].

The dietary compounds may affect different cellular processes. Therefore, short peptides in the diet, particularly tri- and tetrapeptides derived from food proteins, have been shown to inhibit the angiotensin-converting enzyme [61–63]. Other tripeptides with a Pro–His–His sequence have revealed an extraordinary antioxidant

Table 1
Single-nucleotide polymorphisms with an effect on metabolism and nutrition phenotypes

Pathway	Rationale	Genes	SNPs	Disease/trait	Outcome/association	References
Blood pressure	Increased fiber intake improves plasma lipoprotein profile, and has controversial effects on blood pressure. Discrepancies may be due to SNPs in the angiotensinogen gene (*AGT*), which alter blood pressure in response to dietary fiber intake.	*AGT*	M235T	Hypertension	*T235* homozygotes have higher plasma mean angiotensinogen levels and systolic and diastolic blood pressure	[27]
Bone maintenance	*VDR* is crucial in bone metabolism. SNPs associate with high rate of bone loss. Other studies show gene–diet effects involving Ca^{2+} and D vitamin.	*VDR*	C *Taq*I T T *Bsm*I C *poly-A*	Low BMD	*Taq*I associates with caffeine-related risk of bone loss *Bsm*I influences skeletal response to vitamin D *poly-A* is a risk factor for osteoporosis	[28–38]
Lipid metabolism	SNPs within these genes, involved in lipid metabolism and/or transport, affect plasma cholesterol and TG levels in combination with dietary fat intake.	*PPARG* *CETP* *LPL* *APOC3* *APOA1*	Pro12Ala *Taq*I 1595C>G -2854T>G -75G>A	TG and cholesterol HDL and TG TG TG LDL	*Ala12* associates with higher food efficiency *Taq*I increases plasma CETP levels, reduces HDL *1595G* associates with low TG and low CVD risk *2854G* associates with low plasma TG levels *−75A* associates with low LDL levels	[20,39–50]
Antioxidant activity	SOD enzymes are free radical scavengers with important antioxidant activity and SNPs in these genes increase ROS production.	*SOD2* *SOD3* *NOS3*	Ala16Val 760C>G 894G>T	NSCC Low antioxidant defense CAD	*Ala16* associates with higher risk of prostate cancer *760G* allele associates with ischaemic heart disease Associates to increased risk of CAD	[51]
Detoxification	These enzymes are responsible of phase II detoxification and of the DNA adducts' levels after consumption of cruciferous vegetables.	*GSTM1* *GSTT1* *GSTP1*	Deletion Deletion 313A>G 341C>T	Lung cancer	Deletions in *GSTM1*/*GSTT1* associate with reduced risk of developing lung cancer when consumption of cruciferous vegetables is high	[52–54]
Inflammation	SNPs in *TNFα* and *IL-6* have been shown to be proinflammatory. The effect can be modulated increasing dietary levels of omega-3 fats (fish oil).	*TNFα* *IL-6*	−308G>A −174G>C −634G>C	High inflammatory activity	*−308A* SNP alters TNF expression, and associates with cancer susceptibility (stomach, ICC, HCC) and inflammatory diseases (Crohn and CVD) SNPs increase IL-6 levels, predisposing to CVD risk	[55–57]
Folic acid metabolism	SNPs in the genes involved in folic acid metabolism affect plasma homocysteine levels and the balance between DNA methylation and synthesis of nucleotides.	*MTRR* *MTR* *MTHFR*	66A>G 2756A>G 677C>T 1298A>C	Low plasma HCY	High risk of spina bifida and risk for having Down syndrome child Important genetic risk factors in CVD and cancer predisposition	[58]

NSCC, neck squamous cell carcinoma; CAD, coronary artery disease; HCY, homocysteine.

activity [64]. Dietary components were also demonstrated to alter DNA transcription and gene expression via direct or indirect mechanisms. Indeed, food-derived chemicals can follow different but convergent ways: (1) they can be metabolized by primary or secondary metabolic pathways or (2) can enter the cells and act as receptor's ligands altering the intracellular signaling pathways [1,65]. A prolonged fatty acid-rich diet — leading to highest rates of β-oxidation — can alter the intracellular energetic homeostasis, affecting gene expression through changes in the NAD^+/NADH ratio [66]. Moreover, it has been described that the chronic consumption of a maternal high-fat diet results in a 3-fold increase of fetal liver TGs, correlated to nonalcoholic fatty liver disease [67]. These changes are followed by a statistically significant hyperacetylation of fetal hepatic tissue, suggesting that a caloric-dense maternal diet — leading to obesity — epigenetically alters fetal chromatin structure in primates via covalent modifications of histones.

Since it has been demonstrated that dietary chemicals alter epigenetic events, they represent a vivid example of how diet can influence biological processes and phenotypes [68]. Particularly, the DNA methylation status (both hypo or hyper) — crucial in epigenetic events — depends on bioactive food components such as alcohol, folate, fiber, genistein, selenium, zinc and others (see descriptions in Table 2) [66,69,85,86]. DNA methylation can be directly affected by dietary factors, acting in at least four ways. First, dietary components (folate, methionine, choline) may influence the availability of methyl groups, needed for S-adenosyl-L-methionine formation. Second, dietary factors may modify the usage of methyl groups by processes including shifts in DNA methyltransferase activity. A third mechanism may concern the enzymatic activity of DNA demethylation. In the latter hypothesis, different DNA methylation patterns, related to different foods, may influence the response to a specific bioactive food component through a feedback process [69].

Moreover, some dietary chemicals are directly involved in the modification of gene expression acting as exogenous ligands for a class of nuclear receptors of the transcription factor superfamily (discussed below).

Table 2
Dietary chemicals and DNA methylation

Dietary chemical	Mechanism of action	Phenotype/ outcome	Reference
Alcohol	Chronic consumption affects folate metabolism, altering DNA methylation.	Cancer susceptibility	[69–71]
Arsenic	Competes with cytosine DNA methyltransferase and selenium for methyl donation from S-adenosil-l-methionine.	Global hypomethylation in liver	[72]
Choline	Deficiency in the diet has been associated with decreased tissue S-adenosyl-l-methionine.	Hepatic steatosis, cirrhosis and hepatic tumorigenesis	[73]
Folate	Its deficiency has complex effects on DNA methylation depending on cell type, organ and development stage. Depletion alone is a sufficient perturbing force to diminish SAM pools.	Cancer susceptibility	[74]
Genistein	Dietary genistein can mitigate tumorigenic processes via promoter methylation modulation of gene expression.	Mitigates tumorigenesis	[75]
Lycopene	Lycopene has direct DNA demethylating activity. It mitigates tumorigenic processes via promoter methylation modulation of gene expression.	Mitigates tumorigenesis	[76]
Methionine	Its deficiency decreases tissue SAM, resulting in global DNA hypomethylation, and HCC in rodents.	HCC	[73,76,77]
Nickel	Environmental carcinogen; induces de novo methylation of tumor suppressor genes. Suppressive effect on histone H4 acetylation in mammalian cells.	Increased cancer susceptibility	[78,79]
Selenium	Its deficiency decreases DNA methylation. Low intake influences the activity of selenoproteins, causing changes in mRNA levels for the encoding genes.	CVD, cancer susceptibility	[80–82]
Vitamins	Vitamins (B_2, B_6 and B_{12}) are necessary cofactors in the one-carbon (methyl group) metabolism.	A deficiency affect several metabolic pathways	[83,84]

2.3. Nuclear receptors and PPARG gene: the nutrient sensors

It is widely assumed that *micro*- and *macro*nutrients play a key role in the regulation of metabolic pathways and energetic homeostasis, altering the expression of crucial genes. Indeed, the members of the transcription factor superfamily are the main responsible molecules through which the nutrients may influence gene expression [23]. Among these transcription factors, the nuclear hormone receptors superfamily, consisting of about 50 members in the human genome, represents the most important group of molecular effectors of fatty acids and their derivates.

The nuclear hormone receptors have important roles in the regulation of several physiological processes, such as nutrient metabolism, cell proliferation and differentiation [87]. The nutrient-mediated activation of nuclear receptors leads to the induction of different pathways involved in a wide range of cellular functions.

A member of this transcription factor family, namely, the peroxisome proliferator-activated receptor gamma (PPARγ), acts as metabolic nuclear sensor in different cell types — adipocytes, fibroblasts and myocytes — regulating the expression of several key genes involved in glucose metabolism, adipocyte differentiation, lipid oxidation, angiogenesis and inflammation [88,89]. *PPARG* gene encodes different protein isoforms generated by different promoters and alternative splicing [90,91]. The functional role of PPARγ is well documented, and its nucleotide variations have been associated in many studies, even though in a controversial extent, to metabolic diseases such as T2DM, obesity and CVD [92,93]. Nevertheless, the involvement of its polymorphisms in the genetic susceptibility toward complex metabolic diseases is not yet clearly elucidated [94,95].

For instance, Pro12Ala, the well and more extensively studied SNP in *PPARG* gene, has been associated with increased protection to the development of T2DM and insulin resistance [96–100] and, more recently, to decreased incidence of CVD [101]. Ala12 allele has been also associated with a lower body mass index (BMI) in nonobese subjects [96], although the studies are controversial [102–105].

Recent data have shown the interaction of modifying factors, including diet and exercise, with the Pro12Ala SNP in the development and also treatment of T2DM. In the Quebec Family Study, Ala12 allele carriers did not respond to a higher fat intake, whereas, on the opposite, Pro12 allele carriers responded with a gradual deterioration of metabolic parameters, as well as an increase in BMI and waist circumference [106]. This study suggests that the Ala12 allele protects carriers against negative environment influences, such as high-fat diet and lack of exercise.

The functional mechanism of Pro12Ala impact on metabolic disorders is not yet known, although a minor influence on the transcription of PPARγ target genes, has been shown [107]. However, it has been postulated that Pro12Ala SNP may itself not be responsible for the regulation of transcription but could be in linkage *disequilibrium* with a polymorphism in the promoter region [108].

To date, most of the studies have not considered putative polymorphisms in the promoter in association with the Ala12, whereas recent studies have analyzed SNPs in a putative E2 box region in the *PPARG* promoter [92,93], suggesting that further variations should be taken into account for this gene. Although not in the promoter region, a silent SNP, C1431T in exon 6, also known as His477His, has been described in linkage *disequilibrium* with the Ala12 allele [109]. A small number of studies attempted to assess whether common SNPs in *PPARG* are associated with differential response to diets. Cecil et al. [110] demonstrated that responsiveness to dietary components, in terms of body weight, might be genotype dependent. Particularly, *PPARG* genotype is a significant factor in the individual ability to compensate for short-term energy intake, such that 1431T allele was associated with poor energy compensation [110]. Moreover, 1431T allele was associated with poor satiety, mostly explained in the context of leptin secretion and action, representing a potential mechanism by which this nucleotide variant regulates eating behavior. Leptin down-regulation in the adipocytes — mediated by PPARγ agonists — and low leptin levels influence several neuroendocrine responses to regulate and influence energy balance [111].

Overall, these evidences strongly indicate that PPARγ is a direct link between energy balance, control of appetite and adiposity, suggesting this is probably the most critical genetic factor in predisposing to positive energy balance and, ultimately, to obesity.

3. Genes and metabolism: new technological and clinical approaches

Metabolism mainly represents the expression of a balance in the anabolic and catabolic processes. In the past years, the phenotypic expression of metabolic changes has been measured through the

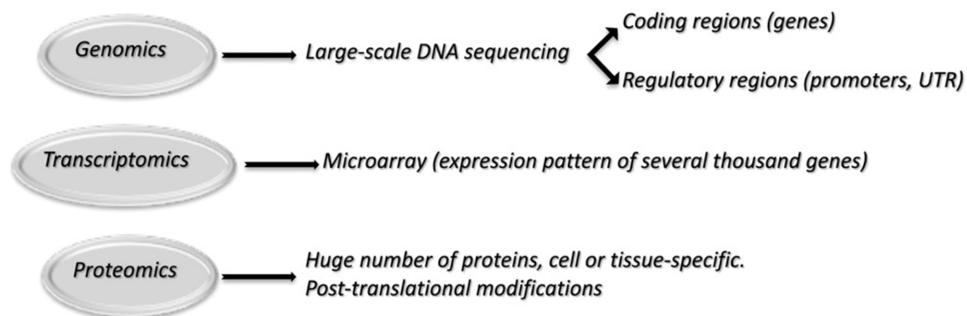

Fig. 2. Novel genomewide approaches in the nutritional genomics.

evaluation of enzyme activity. To date, the genomic revolution has led to the development of novel technologies and molecular tools [112,113], useful for nutritional sciences, allowing a more precise and accurate analysis of biochemical alterations [114].

3.1. Bioinformatics and novel molecular biology techniques

Bioinformatics tools, applied to genomics, proteomics and metabolomics, have already been used for the study of gene–nutrient interactions at cellular, individual and population level [115]. In this postgenomics era, traditional DNA sequencing and genotyping are rapidly shifting toward novel high-throughput approaches, based on microarray technologies, which allow to obtain gene expression profiles of thousands of genes in a single experiment, or proteomics, which currently enables to study the complete collection of proteins in a cell or tissue at any given time (Fig. 2) [116,117]. As advancement in bioinformatics occurs, the importance of changes in mRNA expression should help to predict disease risk and to identify individuals that could benefit from dietary change. This does not mean that mRNA level variations could be useful causal markers, but rather, it might be that a pattern of expressed mRNAs changes in a characteristic and reproducible way [118]. To date, commercial platforms, available for microarray analysis, allow researchers to have a highly reproducible, fast and powerful tool to detect differential gene expression in response to many exogenous stimuli (i.e., dietary components). Discrimination power is a crucial endpoint of this technology. By using probes with different nucleotide length and labeling methods, mRNA detection can greatly improve; the shortest is the probe, and the better discrimination power occurs among highly similar and repetitive sequences. In contrast, the use of longer probes provides a lower extent of discrimination, arisen by a better sensitivity.

Knock-out mice models have often been used in order to identify the mechanisms of action of bioactive dietary components. For instance, the role of some compounds, such as sulforaphane and lipoic acid, on the regulation of gene expression has been studied in rodents. Wild-type and Nrf2-deficient mice fed with sulforaphane have shown several downstream events, providing a more detailed knowledge about the true biological response to this food component [119,120]. In addition to the inability of up-regulating key enzymes, such as glutathione S-transferase, NADP/quinone reductase, gamma-glutamylcysteine synthetase and epoxide hydrolase, the selective block of Nrf2 was also involved in the regulation of xenobiotic metabolizing enzymes, antioxidants and glucuronidation/conjugation pathways. Similar studies have also been performed with $PPARA^{-/-}$ mice, showing the role of this gene in the regulation of lipid metabolism [121]. Furthermore, the effects of lipoic acid on gene expression, in liver cells of rats fed high-fat diet, were evaluated by microarray approach [122]. It was demonstrated that lipoic acid supplementation, resulting in a decrease of lipid peroxidation, plasma cholesterol, TGs and LDL cholesterol, was responsible for the up-regulation of genes related to β-oxidation and free radical scavenger enzymes, whereas those involved in cholesterol synthesis were down-regulated [122].

Few studies have been performed in humans, where an important barrier for the identification of molecular biomarkers is the inaccessibility to tissue samples [23]. A noninvasive source of RNA, to explore gene expression variations in response to human diet intervention, was found in peripheral blood mononuclear cells (PBMCs), suggesting these cells could represent a useful tool to perform nutrigenomics studies [123].

Recently, we have used a similar approach to demonstrate the protective effect of a dietary component, L-arginine, a precursor of nitric oxide, on cultured endothelial progenitors infected with a human pathogen, through the use of microarray analysis [124]. Our results revealed that, as expected, several crucial genes involved in immune and inflammatory response were differentially expressed in cells infected with a human pathogen; interestingly, some of them returned in a steady state when the cells were exposed to sustained doses of L-arginine, thereby suggesting that such a component could be added in the diet to reduce the detrimental effects of a pathogen [124].

Microarray approach was recently used to show a down-regulation of IL-8, a proinflammatory cytokine regulated by ROS, in PBMC after weight loss induced by specific caloric restriction [125]. Interleukin 8 expression decrease was closely associated with the diet-induced reduction in body fat mass, suggesting that IL-8 mRNA levels could be a good indicator of variations in body fat percentage. Another study on gene expression of PBMCs, from healthy humans after fasting, revealed that more than 1350 genes displayed changes at a threshold level of 1.4-fold, and many of them were involved in fatty acid oxidation [126]. By using this approach, a large subset of genes was identified as a molecular target of the nuclear receptor PPAR-α, and these results were also confirmed on ex vivo PBMC.

Although most of the microarray analyses have been performed on animal models or cultured cells, the number of human studies in which microarray has been used to assess the biological effects of dietary chemicals is rapidly growing.

Currently, the most crucial issue in all chip-based mRNA profiling approaches is the analysis of the data sets and their interpretation. These analyses, mainly providing lists of significant genes with related *P* values, are not sufficient to fully understand the underlying biology of metabolic adaptations. A single gene, although significantly up- or down-regulated, does not necessarily have any physiological meaning. The great challenge is how to correctly analyze the wide number of genes, whose expression can be modified by dietary components. The strategy of performing a hierarchical cluster analysis appears to be the most commonly used in order to minimize the significance of a particular gene in explaining the overall response [120].

Moreover, since microarray technologies only give a point-in-time comparison, the "overinterpretation fear" becomes a real possibility. It has been recognized since many years that adaptive processes occur after the ingestion of foods or components in several metabolic pathways. Thus, the quantity and, above all, the duration of exposure to a specific dietary chemical are critical parameters to consider when evaluating one or more sets of microarray data. A further possibility to determine which gene or subset of genes are involved in (or regulated by) the metabolism of dietary components comes from another innovative technique, the RNA interference. By using this technique, investigators systematically disrupt the expression of target genes and observe the resulting phenotype. For instance, this approach has led to the identification of a core set of fat regulatory genes and pathway-specific fat regulators in the worm model system *Caenorhabditis elegans* [127]. Likewise, the same technological approach has been used to identify sites of action of isothiocyanate compounds, such as sulforaphane, arising from broccoli and other related foods [128].

Since transcriptome data, deriving from both microarray and RNA interference techniques, become available, it should be possible to identify molecular targets responsible for metabolic disorders onset, allowing physicians to treat obesity and other detrimental conditions by using foods or their bioactive components.

In response to the availability of high-throughput genome and transcriptome technologies, another promising field of research, the proteomics, has emerged, with the aim of developing and applying methodologies to accelerate the functional analysis of proteins. Usually, the strategies used in proteomics studies can be divided in two main categories with complementary objectives: (1) a global characterization of protein expression in a cell, tissue or organ [129] and (2) the global characterization of protein function. The great potential of proteomics in the nutritional science is the possibility to deliver biomarkers for nutritional intervention and individual disposition, assessing the nutritional status at a molecular level [118]. Combining gene and protein expression profiling represents a useful and complete approach for identifying the effects of dietary components on human cells.

A growing number of studies have employed proteomics, even in combination with microarray analysis, to address biomarkers for diet protection against CVD, inflammation and cancer [130,131]. Nutrient deficiencies, for instance, by force-feeding rats with a zinc-deficient diet, have been used in order to analyze the hepatic transcriptome, proteome and lipidome. By combining these complementary approaches, Dieck et al. [132] show that a zinc-deficient nutritional regimen leads to dramatically altered expression levels of a large number of genes coding for key enzymes in hepatic glucose and also lipid metabolism, thus, causing liver lipids accumulation and chronic hepatic inflammation [132]. Steady-state levels of the mRNAs encoding for enzymes required for hepatic triacylglycerol turnover and β-oxidation of fatty acids were reduced, whereas those of de novo lipogenesis displayed increased levels.

Furthermore, increased vegetable intake was shown to drive a differential gene expression in the colon of healthy mice [133]. The proteomics approach allowed the identification of six proteins with altered expression levels, suggesting a putative protective role in colorectal cancer.

Although these novel technologies and techniques are providing a large amount of useful data to researchers — appearing quite unlimited if considering cell lines or available model organisms — there are evident limitations toward their use in human studies. The analysis of gene expression patterns is restricted by the poor availability of ex vivo vital primary cells or human tissues for analysis, and also by the ethical issues concerning the treatment of human tissues.

However, only a multidisciplinary approach, able to combine all these innovative techniques, will allow researchers and clinicians to understand the effects of single nutrient — or a dietary pattern — on the metabolic behavior of cells, on organs and, in turn, on the whole organism.

3.2. Genetic testing in modern nutrition: is it worth it?

It has been established that nutrition represents the most important, widespread and long-term acting environmental factor, and that dietary components are able to modify, impair or improve the likelihood of developing a metabolic disorder (T2DM, obesity, CVD), exerting their effects on the genetic background. Since the last years, it has been shown that the same dietary recommended guidelines could not be applied to the whole population without inducing massive mistakes [134].

In this *scenario*, the "traditional" nutrition and its limitation for the "classical" dietary approach are slowly being replaced by a "modern" concept of nutrition, turning the attention toward open-minded horizons. In particular, the awareness that responses to a bioactive dietary chemical greatly vary among individuals has claimed much attention to the genetic background and its interaction with nutrients. This evidence has smoothed the way for the spreading of hundreds of companies, taking into account the potential of molecular nutrition research and its long-term goal of tailored nutrition [135]. In particular, direct-to-consumer genetic testing development and purchase represent a rapidly growing market all over the industrialized countries [136]. The idea is that everyone, by easily collecting at home the DNA by rubbing the inside of the mouth with a swab, can receive, in a noninvasive cost-effective manner, information about his own genetic predisposition to develop such a disease (T2DM, obesity, CVD).

To date, the most complete DNA test available examines the individual nucleotide variations — common SNPs and insertions/deletions — in about 30 genes, shown to play major roles in human health, possibly predisposing to the onset of chronic disorders (see for details Table 3). These genes, belonging to different pathways, include detoxification and antioxidant activities, insulin sensitivity, inflammation, tissue repair, bone and cartilage formation/repair, glucose and lipid metabolism. DNA test results are combined to other information derived from a lifestyle questionnaire, resulting in personalized, realistic steps designed to improve and/or maintain the good health status. A personal report that evaluates the current lifestyle, according to the results of the DNA analysis, is what the companies deliver to the genetic test user. It mainly contains dietary recommendations based on the testing results, indicating a specific nutritional supplement advice, the personal diet and lifestyle advice for each tested gene.

However, there are very few randomized clinical trials that actually prove efficacy for any health intervention, and many of them tend to consider the effect of dietary components on a single gene, measuring a biomarker of the disease, rather than considering a disease endpoint [137]. Interesting and exciting preliminary results have been accomplished [122,138–140], but even more studies are needed. Moreover, although in the postgenomic era, it could appear a limitation to examine few polymorphisms in about 1% of the total human genes, an individual whole genome sequence is still too expensive and difficult to analyze [141].

Last but not least, there is a common perception that the results of a genetic test, indicating the possible predisposition to develop a disease, even for nutrition-based pathologies, may cause shock and psychological scars [136]. Very little is known on how people could respond to the results of a direct-to-consumer genetic test that may reveal an increased susceptibility to the onset of complex diseases. The main question is whether awareness of a positive test result would be enough to motivate people to change their lifestyle or would it work in the opposite way.

Table 3
Direct-to-consumer nutrigenetic test sample

Gene pathway	Gene symbol	SNP	Nutritional intervention
Alcohol metabolism	*ADH1B*	Arg369Cis	+
	ADH1C	Arg47His	−
	ALDH2	Ile349Val	+
		Glu487Lys	+
Antioxidant defense	*SOD2*	−28C>T	−
	SOD3	760C>G	+
	PON1	Gln192Arg	+
	EPHX1	Leu55Met	−
		Tyr113His	−
Bone homeostasis	*COLA1*	2046G>T	−
	IL-6	−174G>C;	−
	TNFA	−634G>C	+
		−308G>A	
Ca^{2+} and vitamin D pathway	*VDR*	*Taq*I; *Fok*I	+
		*Bsm*I	−
Cholesterol metabolism	*APOA5*	−1131T>C;	+
	CEPT	56C>G	−
	LPL	279G>A	−
	LIPC	1595C>G	+
		−250G>A;	
		−514C>T	
Folic acid metabolism	*MTHFR*	677C>T;	+
		1298A>C	
Glucose/lipid metabolism	*PPARG*	Pro12Ala	−
Homocysteine removal and vitamin B_6 metabolism	*MTR*	2756A>G	−
	CBS	699C>T	−
Inflammation	IL-6	−174G>C	+
	TNFA	−308G>A	+
Phase I detoxification	*CYP1A1*	2455A>G	+
	CYP1A2	1B; 1E; 1F	+
Phase II detoxification	*GSTM1*	deletion	+
	GSTP1	313A>G;	+
	GSTT1	341C>T	+
		deletion	
Salt sensitivity	*AGT*	Met235Thr	−
TG metabolism	*APOC3*	3175C>G	+
Vascular/heart function	*ACE*	Deletion	+
	NOS3	894G>T	+
Vitamin B_{12} metabolism	*MTRR*	66A>G	+

The table shows the genes and the nucleotide variations within these, screened by common direct-to-consumer nutrigenetic tests. The effect of a specific SNP may be protective or predisposing toward the onset of a disease phenotype. The presence of a so-called protective gene variant does not require any nutritional supplementation (indicated as "−" in the table). On the opposite, in the presence of a predisposing SNP, detailed, genome-tailored nutritional — and lifestyle — recommendation are provided to the consumer (indicated as "+" in the table).

3.3. Copy number variations: impact on human common disorders and perspectives

Genetic variations in the human genome may take many forms, from wide microscopically visible chromosome abnormalities to single-nucleotide changes [142]. Recently, several studies have disclosed many submicroscopic copy number variations (CNVs) of DNA fragments, ranging from kilobases to megabases [142–146]. Innovative molecular technologies have confirmed that most of individuals carry far higher than expected numbers of CNVs, many of which have not been detected by previously used mutation detection or cytogenetic techniques [147]. Large deletions, insertions and duplications, collectively termed *CNVs*, or copy number polymorphisms, have been found in all humans and primates [148,149].

Copy number variations have emerged as a dominant force, determining both genetic and phenotypic variations [145]. Currently, it has been estimated that in terms of total number of base pairs of genetic difference between two individuals, CNVs contribute approximately twice the amount than SNPs [150,151]. Variations in gene copy number and gene fragments lead to multiple effects on phenotype [152]. It is interesting to note that most of CNVs appear to be enriched within genes involved in molecular–environmental interactions, possibly influencing immune defense and disease susceptibility of humans [153].

CNVs may contribute to human disease in several different ways [147,148]. It has been postulated that CNVs may act by directly affecting gene dosage and gene expression. Thus, due to their effect on gene dosage, CNVs are unlikely associated with mendelian diseases, whereas it is more likely they play a role in late onset diseases or more complex common diseases [154]. Moreover, evidence indicates that CNVs are associated with immunological or environmental sensor genes [149], thereby suggesting that variation in gene expression may directly play a role in complex diseases. For example, CNVs can cause statistically significant changes in mRNA levels of a catabolic enzyme, associated with nutrient intake in humans [155].

Particularly, to date, there is only one published study assessing a direct relationship between gene copy number and the amount of encoded protein. Indeed, Perry et al. [155] have recently demonstrated that human salivary amylase gene, *AMY1*, which has extensive CNVs [143,156], shows a characteristic pattern of expression, consistent with a history of diet-related selection pressures, depending on starchy food consumption of humans. However, although *AMY1* locus is one of the most variable in the human genome, recent genomewide analysis identified about 1500 CNVs among 270 phenotypically normal individuals [142], and many more are likely to be discovered.

Thus, it is reasonable to hypothesize that, as well as documented for the *AMY1* gene, strong diet-related selection pressures may have influenced, through gene CNVs, several other genes along the human genome evolution.

4. Conclusions

Past and also current dietary guidelines do not consider the differences in the individual response to a diet, reflecting an impaired efficacy of these dietary recommendations. In the last decade, nutrigenomics has claimed the possibility of reaching substantial advances in public health through a low-cost approach of preventive medicine. Adjusting human metabolism using the diet in a "genome- and age-specific" way, without the support of any drug, may minimize the risk and the onset of several degenerative diseases associated with ageing, decreasing public health costs.

To date, a growing number of studies have described SNPs that modulate the individual response to a specific dietary compound, explaining how gene–diet interactions influence the metabolism. Furthermore, the postgenomic revolution and the development of innovative genomewide technologies and molecular tools for rapid genetic testing have led, also in the nutritional science, to more accurate and promising analyses. However, although current evidence, from basic research and ongoing clinical trials, has shown that the analysis of nutrient–gene interactions represents a promising field, it is not enough to start making specific tailored nutritional recommendations based on individual genetics. It is critical that preliminary studies, briefly summarized in this review, undergo further replication in many populations. This purpose must be addressed through wider and better-characterized population studies, considering an adequate size, in order to have sufficient statistical power. Moreover, careful attention should be addressed to genotype/phenotype correlation. This imperative could be achieved only with the collaboration of experts in different fields, ranging from biologist and bioinformatics to food and nutrition professionals [157]. Moreover, traditional nutrition scientists should understand the potential of molecular nutrition research in animal models to provide insights into human nutrition. Finally, food industry should recognize, and take into account, the promising steps and the always

more relevant role of nutrigenomics in developing an evidence-based nutrition.

In conclusion, we believe that in the coming years, most of the individuals affected by chronic metabolic disorders, displaying dramatic heterogeneity in response to the recommended therapeutic diets, will benefit from individually adjusted dietary recommendations. A modern concept of nutrition, based on a deep and complete individual genetic and molecular knowledge, will represent the only viable way to reach this future perspective.

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