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REVIEW ARTICLE

Nutrigenetics—personalized nutrition in obesity and cardiovascular diseases

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Abstract

Epidemiological data support the view that both obesity and cardiovascular diseases (CVD) account for a high proportion of total morbidity and mortality in adults throughout the world. Obesity and CVD have complex interplay mechanisms of genetic and environmental factors, including diet. Nutrition is an environmental factor and it has a predominant and recognizable role in health management and in the prevention of obesity and obesity-related diseases, including CVD. However, there is a marked variation in CVD in patients with obesity and the same dietary pattern. The different genetic polymorphisms could explain this variation, which leads to the emergence of the concept of nutrigenetics. Nutritional genomics or nutrigenetics is the science that studies and characterizes gene variants associated with differential response to specific nutrients and relating this variation to various diseases, such as CVD related to obesity. Thus, the personalized nutrition recommendations, based on the knowledge of an individual's genetic background, might improve the outcomes of a specific dietary intervention and represent a new dietary approach to improve health, reducing obesity and CVD. Given these premises, it is intuitive to suppose that the elucidation of diet and gene interactions could support more specific and effective dietary interventions in both obesity and CVD prevention through personalized nutrition based on nutrigenetics. This review aims to briefly summarize the role of the most important genes associated with obesity and CVD and to clarify the knowledge about the relation between nutrition and gene expression and the role of the main nutrition-related genes in obesity and CVD.

Introduction

Obesity is an emerging noncommunicable disease associated with chronic low-grade inflammation, and the development of many obesity-related diseases, such as cardiovascular disease (CVD), type 2 diabetes mellitus, and a number of cancers [1]. Obesity has a multifactorial etiology, where lifestyle factors, including unhealthy dietary patterns, physical inactivity, and poor sleeping habits, are recognized to play a crucial role in both the development and progression of obesity and its comorbidities [1]. Nevertheless, in the so called obesogenic environments, up to 70% of the population variation in obesity may be attributed to genetic factors [2]. In this very complex scenario, there is growing evidence that the evaluation of gene–diet interactions in relation to obesity and CVD could currently represent an interesting field of application for innovative nutritional interventions for changing health behaviors.

The nutrigenetics is the science that explores the specific interactions between genes and nutrients and relating this variation to human health and to variable disease states, including obesity and CVD [3]. To date, through Genome-wide association studies (GWAS), the Human Genome Project has led to sequencing the entire human genome in order to identify genes and/or loci associated with a specific

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phenotype [4, 5]. The Human Genome Project led to the understanding of multiple mutual relations among genes, nutrition, and diseases [6]. In fact, the sequencing of the human genome has reported a significant genetic heterogeneity within the same human population groups. A number of single-nucleotide polymorphisms (SNPs) can have a relation to nutrition [7]. There is a bidirection relationship between genome and nutrition that may affect the individual's diseases susceptibility [8]. In particular, on the one side, the genetic background of one person can define the metabolic response, nutritional state, and the susceptibility to nutrient-dependent or related diseases [9]. On the other side, the nutrients up- or downregulate the gene expression, and consequently, at the molecular level, the metabolic responses. These interactions between nutrition and genome have led to two new science branches, nutrigenetics and nutrigenomics [10]. However, it has to be underlined that the genetics can explain only a small part of the total variance of factors associated with CVD [5, 11].

In this context, specific nutrients, through the interaction with individual genetic characteristics, may lead to the up- or downregulation of specific metabolic pathways, which may contribute to the development of obesity and CVD [5]. The nutrigenetics studies provide the evidence of the association between SNPs and single nutrients. As an example, it has been previously reported higher high-density lipoprotein (HDL) cholesterol levels in carriers of the A allele for an SNP located in the promoter region of Apolipoprotein (APO) A1 after a diet rich in poly-unsaturated fatty acids (PUFA) [12]. Similarly, the APO E polymorphisms, in particular the carriers of APO E4 isoform, have been associated with a higher risk of CVD and the carriers of these polymorphisms have a 46% increase in CVD risk compared with the carriers of the APO E3 isoform [13].

Beyond single nutrients, it is worthwhile to consider that the diet is a complex combination of several nutrients and foods with similar properties, thus it is very challenging, to separate the effect of a single nutrient from others, in free-living populations [14]. Very recently, the Food4Me project, a large randomized trial of 5562 European participants, investigated the hypothesis of personalized nutrition based on an individual's genetic background [15]. The objective of this study was to investigate the effectiveness of three different types of dietary interventions. For this purpose, participants were randomly assigned to one of the following intervention groups for a 6-month period: diet based on the healthy eating guidelines, diet based on both the individual's dietary intake and anthropometric measurements, including body mass index and waist circumference, and diet based on both anthropometric measurements and the individual's dietary intake, and in addition on genotypic data, in particular related to five genetic variants in obesity-associated gene (FTO), fatty acid desaturase (FADS)-1, transcription factor 7-like 2, APO E, and methylenetetrahydrofolate reductase (MTHFR) [15]. In particular, the results of the Food4Me randomized controlled trial investigated the effect of the APO E genotype on response to the personalized dietary advice intervention. Data from this trial showed that the diet based on genotypic data resulted in a higher reduction of saturated fatty acids intake for the gene-based personalized nutrition targeted to APO E compared with standard dietary advice [16], and suggested this approach could improve the nutritional behavior, with favorable healthy consequences in the long term [16]. In particular, it is also remarkable to notice that the effect of adherence to a Mediterranean style diet on incidence of cardiovascular outcomes in type 2 diabetes [17–19] is also mediated by genetic influences.

Offering personalized diet advice based to the individual's genetic susceptibility could be a promising strategy for preventing or treating obesity and obesity-related diseases, including CVD. Tailored dietary advice is the objective of precision nutrition, which is based on the study of nutrigenetics in order to identify the specific genetic factors able to explain the interindividual variability of the response to a specific dietary pattern [20]. To promote nutrigenetic studies, it is mandatory to increase the knowledge on this topic and to develop useful dietary and lifestyle recommendations to manage body weight and reduce CVD risk. Indeed, personalized nutrition recommendations based also on the individual's genetic background might improve the outcomes of a specific dietary intervention and could represent a new dietary approach to prevent nutrition-related diseases and obesity complications. Given these premises, it is intuitive to understand that the elucidation of diet and gene interactions could support more specific and effective dietary interventions in both obesity and CVD prevention through personalized nutrition based on nutrigenetics. This review aims to briefly summarize the role of the most important genes associated with obesity and obesity-related CVDs.

Obesity and cardiovascular diseases (CVDs)

Obesity represents a major risk factor for CVD. One of the most important consequences of obesity is a widespread impairment of cardiovascular physiology as a result of structural and functional adaptations induced by obesity [21]. These adaptive mechanisms translate into profound hemodynamic alterations due to increases in blood volume, cardiac output, stroke volume, and heart rate, resulting in a progressive cardiac remodeling, in terms of left atrial enlargement, left ventricular (LV) dilation [22], and eccentric or concentric LV hypertrophy [23, 24].

It has been widely established that the excess of adipose tissue exerts a number of endocrine influences, including synthesis and release of hormones and cytokines [25]. Some of the latter, named adipokines, orchestrate several pathways related to the development of the well-known chronic low-grade inflammation which, in turn, is strongly related to the increased risk of CVD development [26] through its proatherogenic effect [27].

The excess of adipose tissue increases the epicardial adipose tissue (EAT) deposition that in turn has been recognized to play a pivotal role in the development of cardiovascular complications related to obesity [21]. Increased EAT is responsible for a local proatherogenic effect, resulting in increased risk of coronary heart disease and arrhythmias, including atrial fibrillation [28].

Interestingly, obesity-related alteration of the gut microbiota is responsible for triggering several inflammatory pathways, resulting in increased cardiometabolic risk [29], and production of metabolites related to cardiovascular risk. Emerging evidence, indeed, focused the attention on the trimethylamine N-oxide (TMAO), as a gut microbiota-derived metabolite recognized as a prognostic marker for obesity-related cardiovascular events beyond traditional risk factors [30]. In particular, scientific evidence demonstrated TMAO as a risk factor for atherosclerosis [31], stroke [32–35], and heart failure [36]. A recent study demonstrated a positive association between TMAO serum levels and both Visceral Adiposity Index and Fatty Liver Index as a gender-specific indicator of adipose dysfunction and predictor of nonalcoholic fatty liver disease, respectively [37].

Nutrigenetics for CVD prevention in patients with obesity

Over the past century, research established that lifestyle, including diet, strongly affects CVD risk [38–40]. For this reason, dietary recommendations have been the focus of public health campaigns aiming to reduce CVD risk [40–42]. Despite that effort, the expected reduction of mortality for CVD does not occur consistently, and this failure has been attributed, at least in part, to individual variability to dietary recommendation responsiveness and to different genetics, or possibly to the bidirectional interactions between both factors. The Human Genome Project [43] highlighted a plethora of genes and their end products, the proteins, which could be involved in these differential weight responses to diet. Nutrigenetics is the discipline that studies how genetic variability regulates individual differential responses to dietary regimens. It can be considered as a section of nutrigenomics, which, more widely, investigates interactions between nutrients and the genome [44], taking into account not only genetics, but also gene expression changes and epigenetics. Relevant improvements in the fields of nutrigenetics and nutrigenomics opened the possibility for personalized nutrition aimed to prevent major diseases, including CVD.

Epidemiologic studies demonstrated that a strong predisposition to CVD is due to individual genetics. Numerous familial and twin studies [45] supported this notion, together with large long-term cardiovascular cohort studies [46, 47]. GWAS identified dozens of genes/loci associated with atherosclerosis, many of which have been confirmed by independent investigations. Despite that, only about 30% of the estimated heritability variance could be explained by the identified susceptibility alleles [48]. To clarify the origin of this missing heritability, several limits of genetics studies have been hypothesized to be involved: lack of consideration of gene–gene interactions, limited study power to detect rare variants, and contribution of environmental factors, including nutritional habits among others.

Given these premises, it is intuitive to understand that the elucidation of gene–diet interactions could support more specific and effective interventions for CVD preventions through personalized nutrition. Nutrigenetics, indeed, focusing on genetic variants able to explain differential responses to nutrients and/or dietetic interventions, can play a role in the prevention of cardiovascular events.

As previously mentioned, several studies highlighted that a substantial heterogeneity in response to dietary intervention actually exists, according to the different dietary component included [49–53], and molecular genetics, as soon as it developed, was addressed as the tool able to explain that variability. On the other hand, dietary reference values, such as the recommended dietary allowances, are designed for the general population assuming a Gaussian distribution of the different metabolic outcomes ensuing nutrients intake. Due to their different genetics, these reference values are not optimized for population subgroups, which may substantially diverge in the activity of transport proteins for a certain nutrient or in the activity of enzymes necessary to metabolize that micronutrient or requiring it as a cofactor. Despite a single SNP may have a relatively small effect in comparison with other known risk factors (such as family history for CVDs), several minor genetic variances in association with various environmental exposures (i.e., inadequate diet) could result in relevant changes in gene expression. As a result of the interactions between all these variables, the final phenotype could be affected by negligible changes or, on the contrary, by an increased risk due to the co-existence of these unfavorable conditions. This setting could be particularly alarming when involving pathways potentially able to promote atherogenesis (i.e., inflammation and/or lipid metabolisms) in high-CVD risk subjects, such as patients with obesity.

While nutrigenetic studies were almost all observational in the first era of this discipline, the number of interventional investigations including genetic variability for dietary responsiveness significantly increased in the last decades [54]. This aspect is noteworthy considering that one of the most popular accusations that skeptical researchers/physicians addressed to nutrigenetics and nutrigenomics was that clinical advice based on molecular nutrition was deduced by observational studies rather than interventional [55]. In this context, recent evidence coming from interventional studies involving nutrigenetics has identified specific pathways as potentially involved in heterogeneous dietary responses and consequentially able to promote or prevent CVD in susceptible patients.

Genetic variants affecting responsiveness to nutritional intervention tailored to reduce CVD risk in patients with obesity

The following paragraph describes genetic contributions to pathways that should be considered to tailor personalized dietetic recommendations to prevent CVD in patients with obesity. Herein, we report recent evidence supporting the relationship between genetic variants and responsiveness to specific nutrients intake. In particular we focused on both observational studies and clinical trials (summarized in Table 1) investigating the effects of nutrients supplementation on cardiovascular outcomes, with the aim to identify applications of nutrigenetics in clinical practice. Graphical representation of personalized interventions tailored to reduce CVD risk in obese patients based on their individual responsiveness to specific nutrients or dietary plans are reported in Fig. 1.

Omega-3 fatty acids

Perturbed lipid metabolism and inflammation (which are both strongly associated with dietary patterns) [56, 57] are key players in atherosclerosis onset. Indeed, many of the identified genetic variants associated with CVD are mapped to genes directly or indirectly involved in the regulation of these two central pathways.

Numerous investigations about nutrigenetics and lipid metabolism regulation have been conducted [58]. Definitely the homeostasis of lipid profile depends on the interplay of intricate biochemical pathways involving several different enzymes, receptors, and other factors, through which the genetic variability could modulate the final lipid phenotype. These individual differences have not been considered in the guidelines to the general population, and this is reflected in the heterogeneous responses observed after nutritional interventions aimed to improve lipid profile.

Particularly relevant, both in terms of lipid profile regulation and inflammation reduction, is the intake of PUFA (i.e., omega-6 and omega-3 fatty acids), which has been linked to decrease in CVD risk. It has been extensively demonstrated that omega-3 fatty acids (eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA) above all) exert cardioprotective effects through reduction of triglyceride levels, by contrasting the pro-inflammatory eicosanoid storm, and decreasing platelet aggregation and blood pressure. However, intake of omega-3 fatty acids does not have the same effect in every subject. Indeed, genetic variations in the long-chain PUFA biosynthetic pathways affect levels of circulating and tissue PUFA together with other biomarkers and clinical endpoints of CVD. A comprehensive review of the diet–gene interactions and PUFA metabolism [59] describes as particularly relevant for CVD the genetic variations within the fatty acid desaturase *FADS* gene family (in particular *FADS1* and *FADS2*, involved in the bioconversion of essential fatty acids to longer chained PUFA), fatty acid elongase (*ELOVL2)* (involved in DHA biosynthesis), phospholipase A (*PLA2G4*), and arachidonate 5-lipoxygenase (*ALOX5*) (that code for enzymes that mobilize and metabolize arachidonic acid). O'Neill and Minihane [60] summarized the existing evidence of *FADS* genotype influences on fatty acid status and cardiovascular health [60]. Current evidence demonstrates that carriers of *FADS* minor alleles have higher plasma and tissue levels of linoleic and α-linolenic acids, lower levels of arachidonic acid, EPA, and also lower level of DHA. This induces a reduced inflammatory status and CVD risk, and dietary total fat intake can modify this association. Despite the fact that effect size of this gene *x* nutrient interaction has not been measured, the authors suggested the usage of this genetic information to refine EPA and DHA recommendations (with higher intake recommended for *FADS* minor alleles carriers) [60].

Clinical trials investigating the different responsiveness to omega-3 supplementation focused on various gene variants, including cluster of differentiation (*CD)36* [61], nitric oxide synthase *(NOS)3* [62], peroxisome proliferator-activated receptor gamma (*PPARG*) [61], *ALOX5* [63], *APOE4* [64], free fatty acid receptor (*FFAR)4* [65], and genes associated with triglycerides response to omega-3 supplementation [66]. More specifically, people with diabetes carrying the following alleles *CD36-G, NOS3-A*, and *PPARG-G* are better responders to omega-3 supplementation in the improvement of lipid profile [61]. In elderly people carrying the gene variant *APOE4*, supplementation with omega-3, significantly reduces the expression of genes related to interferon [64].

Further studies have been conducted on healthy individuals. Although these people are not at high-CVD risk, these studies are useful to elucidate the different role of

Table 1 Evidences from clinical trials.

Reference	Study design	Population	Gene variants	Outcomes
Omega-3 supplementation				
[61]	DB, R, PC	Type 2 diabetics	CD36 (rs1527483), NOS3 (rs1799983), PPARG (rs1801282)	Diabetic CD36-G allele, PPARG-G allele, and NOS3-A allele carrier are better responders to omega-3 supplementation in improvement of lipid profile
[63]	DB, PC	Healthy subjects	ALOX5; genotypes: "dd," "d5," and "55" ("d" represents the deletion of 1 or 2 SP1 binding sites; "5" indicates the allele with 5 sites)	Increased levels of EPA, DHA, and omega-3 and reduced omega-6/omega-3 ratio and HDL particle concentrations in "d5" and "55" genotypes. Reduced TG in "d5" genotypes
[64]	DB, R, PC	Elderly	APO E4	The expression of genes related to IFN is reduced only in carriers
[65]	DB	Healthy subjects	12 tagging SNPs in FFAR4	Omega-3 supplementation reduce HOMA-IR and fasting insulin in carriers of the major allele of several FFAR4 SNPs
[66]	DB	Healthy subjects	31 SNPs in 6 genes associated with TG response to omega-3 supplementation	Variant carriers are nonresponder to omega-3 supplementation for control of TG serum levels
Folate supplementation				
[76]	DB	Subjects with hyperhomocysteinaemia	MTHFR and MTRR	SNPs rs1801133 and 1801131 in MTHFR and rs1801394 and rs162036 in MTRR are associated with the efficacy of folate supplementation for hyperhomocysteinaemia
Vitamin D supplementation				
[83]	DB	Type 2 diabetics	VDR polymorphism	Significantly improvements of metabolic profile in Taq-I GG genotype and Bsm-I TT genotype carriers
[84]	DB, R, PC	Postmenopausal women	SNP rs11185644 in RXRA	SNP in RXRA are associated with vitamin D3 dose-response
[85]	DB, R, C	Type 2 diabetics	Fok-I: alleles are defined as "F" (absence of the restriction site) or "f" (presence of the restriction site)	After supplementation, differences in 25(OH)D serum levels were significant between "ff" and "FF." In "FF" carriers lower levels of inflammatory biomarkers were detected compared with "ff" and "Ff." "ff" carriers are "low responders" to supplementation with 25(OH)D

DB double-blind, *R* randomized *PC* placebo-controlled, *C* controlled, *OL* open label, *EPA* eicosapentaenoic acid, *DHA* docosahexaenoic acid, *HDL* high-density lipoprotein, *TG* triglycerides, *HOMA-IR* homeostasis model assessment of insulin resistance, *IFN* interferon, *SNP* single-nucleotide polymorphism.

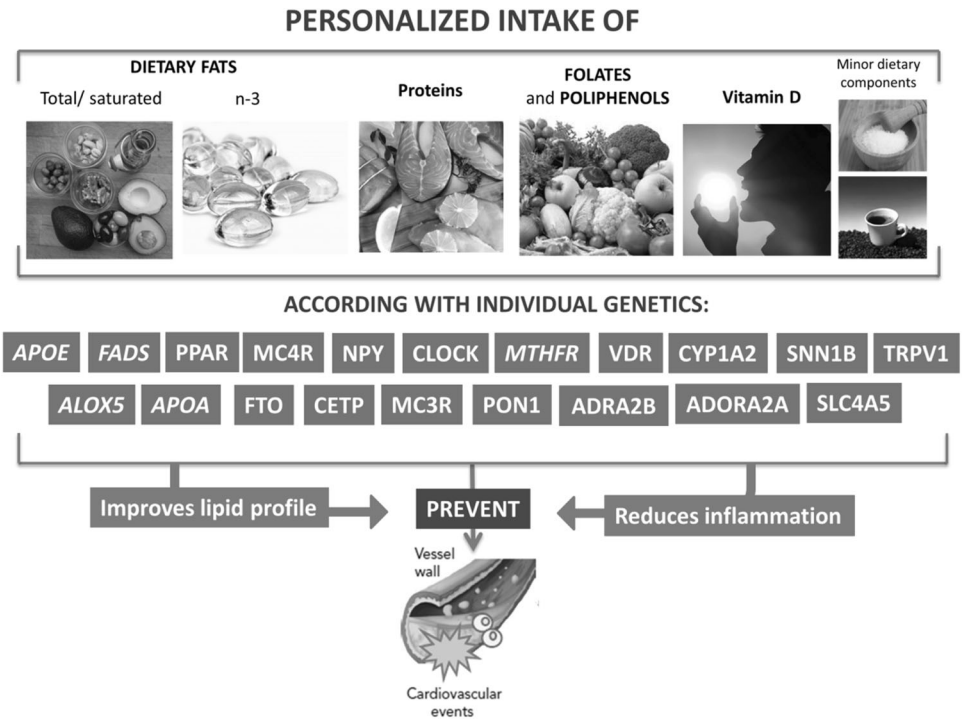

Fig. 1 Nutrigenetics-personalized nutrition in obesity and cardiovascular diseases. Graphical representation of personalized interventions tailored to reduce CVD risk in obese patients based on their individual responsiveness to specific nutrients or dietary plans. A personalized diet based on nutrigenomics lead to both improvement lipid profile and reduction of inflammation, and could act on cardiovascular prevention in patients with obesity.

omega-3 supplementation on the basis of genotype on cardiovascular outcomes. Armstrong et al. [63] studied three different genotypes indicated as "*ALOX5-dd*," "*ALOX5-d5*," and "*ALOX5-55*", where "d" represents the deletion of one or two SP1 binding sites and "5" indicates the allele with five sites in 98 subjects. After 6-week treatment with 5 g fish oil daily, increased levels of EPA, DHA, and omega-3 and reduced omega-6/omega-3 ratio and HDL cholesterol particle concentrations were observed in "d5" and "55" genotypes; in addition, reduced serum levels of triglycerides were observed in "d5" genotypes [63]. More recently, in 208 subjects treated with 5 g fish oil for 6 weeks, Vallée Marcotte et al. identified 31 SNPs in six genes related to control of triglyceride levels in response to supplementation with omega-3 fatty acids that confer non-responsiveness to treatment [66]. Interestingly, the same research group previously demonstrated that supplementation with 3 g omega-3 fatty acids daily for 6 weeks significantly reduced insulin resistance and fasting insulin in carriers of the major allele of several *FFAR4* SNPs [65].

Folate

It is well known that both micronutrient deficiency and abundance can alter the genome stability, thus impacting nutrient–nutrient and gene–nutrient interactions (which is influenced by the genotype) [67]. SNPs can influence micronutrient status and chronic diseases related to their metabolism. Consequently, (micro)nutrients have the potential to increase or reduce the chances of disease onset through regulation of these interactions.

A pivotal example is the regulation of homocysteine levels by folate intake. Plasma homocysteine is an integrated marker of one carbon metabolism and is inversely correlated with folate, vitamin B6 and B12 intake, while it is positively associated with alcohol consumption [68]. The accumulation of homocysteine is a predictor of CVD risk [69, 70]. Several mechanisms have been postulated to promote CVD onset, and promotion of inflammation is one of them [71]. Plasma homocysteine has a heritability estimate of 8–57% [72, 73]. One of the most investigated variants associated with increased plasma homocysteine is the C677T polymorphism (rs1801133) in 5,10 MTHFR gene. Carriers of the T allele display reduced ability to convert methylenetetrahydrofolate to methyl-tetrahydrofolate, which is responsible for the impairment in the homeostasis of the one carbon cycle pathway [74]. A recent meta-analysis confirmed that not only TT genotype is associated with higher plasma homocysteine levels and lowered serum folate, but also to a reduced response to short-term folate supplementation [75]. These data support the necessity to identify MTHFR TT carriers in order to ensure them an adequate folate intake able to override genetic effects (that could lead them to increased risk to develop CVD) minimizing any adverse outcomes. Indeed, it has been demonstrated that efficacy of hyperhomocysteinaemia treatment with folate supplementation depends on MTHFR genotype [76].

A prospective cohort study was performed on subjects with hyperhomocysteinaemia in order to evaluate how polymorphisms of genes related to folate metabolism change the efficacy of supplementation with folic acid [76]. Subjects were administered 5 mg folate daily for 90 days and homocysteine levels were measured before and after treatment. In addition, SNPs in *MTHFR* and *MTRR* genes were evaluated. After treatment, the efficacy of folate supplementation in reducing homocysteine levels was higher in participants carrying the SNPs rs1801133 and rs1801131 in *MTHFR* and rs1801394 and rs162036 in MTRR [76].

Vitamin D

Another micronutrient whose homeostasis is important to prevent CVD is vitamin D. While deficiency of this vitamin was previously related mainly to skeletal complications (osteoporosis, osteomalacia, osteopenia, and bone fractures), recent evidence reported that vitamin D deficiency has been associated to several nonskeletal diseases such as cancer, neurological disorders, metabolic diseases, and CVD [77]. Indeed, a meta-analysis involving 65,994 participants demonstrated a linear and inverse association between circulating vitamin D levels and CVD risk [78], supporting the hypothesis that vitamin D levels should be taken into account when planning a dietary regimen aimed to prevent CVD risk. This issue appears as particularly relevant in the obese population, which is not only more prone to CVD, but also to vitamin D deficiency (vitamin D deficiency prevalence is 35% higher in patients with obesity than in the eutrophic population) due to vitamin D lipophilic properties [79]. Despite circulating 25-hydroxy vitamin D concentrations being mainly determined by sun exposure followed by diet [80], growing evidence suggests that genetic factors could also play a role in determining vitamin D levels. A genome-wide association study identified some common genetic determinants of vitamin D insufficiency (rs2282679, rs12785878, rs10741657, and rs6013897) near to genes regulating cholesterol synthesis, hydroxylation, and vitamin D transport [81]. Furthermore, several SNPs located in the gene encoding for the vitamin D receptor (VDR) (*Taq-I*, *Bsm-I*, *Apa-I*, and *Fok-I*) [82] were also associated with different responses to vitamin D treatment [83]. Therefore, a nutrigenetic assessment could represent an additional tool to tailor vitamin D supplementation in order to prevent CVD.

The different response to vitamin D supplementation on the base of gene variants has been investigated in postmenopausal women with overweight and obesity [84] and in people with obesity and type 2 diabetes [83, 85]. Recent evidence suggests that SNPs in the vitamin D-related receptor genes are responsible for a different response to treatment. In particular, in 2207 postmenopausal women with overweight and obesity, the SNP rs11185644 in retinoid X receptor alpha (*RXRA*) has been demonstrated to be significantly associated with dose–response variation of 25 (OH) serum levels to vitamin D supplementation [84]; in 204 people with type 2 diabetes, *VDR* polymorphisms have been investigated, showing that supplementation with 2000IU vitamin D daily for 12 months significantly improved the metabolic profile in *Taq-I GG* and *Bsm-I TT* genotype carriers [83]. Moreover, Neyestani et al. studied the different response to vitamin D in 140 people with type 2 diabetes carrying the *VDR* polymorphism *Fok-I*, the alleles of which have been defined as "F" (in case of absence of the restriction site) and "f" (in case of presence of the restriction site). After 12 weeks of treatment with 500 IU vitamin D/day, significant differences in 25(OH)D serum levels have been noted between "ff" and "FF," in particular, the higher increment in serum 25(OH)D was found in "FF" (25(OH)D serum levels increment: FF > Ff > ff). Interestingly, lower levels of inflammatory biomarkers, including c-reactive protein and interleukin-6, were detected in "FF" carriers compared with "ff" and "Ff." The authors, thus, conclude that "ff" carriers are "low responders" to vitamin D supplementation [85].

Dietary pattern

Extending the inquiry about fat intake and CVD, it is interesting to pay attention to the diatribe between low-fat and low-carb diets, which has recently become a hot topic in dietetics. In fact, while low-fat diets have been strongly promoted as antiatherogenic during the last decades, interesting evidence about use of low-carb diets is recently emerging [86]. Several nutrigenetic studies, with the inclusion of different genetic alleles, discussed the use of high-fat or low-fat diets in tailored nutritional approaches aimed to improve weight loss, lipid profile, and glycaemic control [87–91]. Most of the investigated genes were related to food intake control and regulation of energy homeostasis (i.e., *FTO* and *MC3R*) or glucose and lipid metabolism (i.e., *ADIPOQ* and *CETP*) [89, 92, 93]. Interestingly, genetic variants in the *FTO* and *MC4R*, both associated with appetite and food craving, have also been investigated for differential satiety in response to dietary protein intake [94, 95]. Heterogeneous responses after low energy diets were also observed in terms of weight loss and inflammation reduction according to *FTO, PPAR*, and *NPY* [96, 97], suggesting that different dietetic regimens in terms of macronutrients should be optimized to effectively reduce inflammation and improve lipid profile in subjects with different genetic backgrounds.

In addition, other nutrigenetic studies have reported some individual variations in the response to the Mediterranean diet [98–100]. Among dietary patterns, the Mediterranean

diet is considered one of the healthiest in the world [101]. The Mediterranean diet is characterized by a high consumption of healthy food (e.g., extra virgin olive oil, fish, fruits and vegetables, legumes, unrefined cereals) [101]. This dietary pattern plays a key role not only in the prevention of a number of chronic diseases, including CVD and metabolic syndrome [102, 103], but in providing an important contribution to weight loss [104], contributing to prevent and treat obesity [105]. It is remarkable to notice that it has been recognized that the effect of adherence to the Mediterranean diet on cardiovascular outcomes [17–19] or others [106, 107] is also modulated by genetic influences (i.e., SNPs located in the genes *NLRP3*, *CLOCK*, *MC4R*, *FTO*, and *PPAR*). Garaulet et al., in a total of 1287 people with overweight and obesity, analyzed the anthropometric measurements and PERILIPIN1 (PLIN1) genotypes, including 6209T>C (rs2289487), 11482G>A (rs894160), 13041A>G (rs2304795), and 14995A>T (rs1052700) after the Mediterranean diet and weight-loss progression. The PLIN1 locus was associated with variability in response to a weight-loss program based on a Mediterranean diet. In particular, carrying the minor C allele at the PLIN1 6209T>C was associated with a better weight-loss response ($p = 0.035$) after 28 weeks of treatment and the probability of being a better responder evaluated as percentage of weight loss ≥ 7.5%, was 33% higher among C than among TT carriers ($p = 0.017$) [98].

The Food4Me Study demonstrated the beneficial effects of higher adherence to the Mediterranean diet after 6 months, also in the presence of an elevated genetic risk evaluated with a Genetic Risk Score, on anthropometric and biochemical markers. In particular, the authors found a greater reduction in body mass index and plasma glucose levels in the participants with a high genetic risk score when they had a higher adherence to the Mediterranean diet [99].

Very recently, Di Renzo et al., on a sample of 188 people divided into two groups, control group, and Mediterranean diet group, analyzed the FTO rs9939609 allele and the difference in body composition at baseline and after 4-week nutritional intervention in order to see if the FTO polymorphism could influence the response to a Mediterranean diet treatment [100]. The authors found significant relations of the variation of total body fat with the diet–gene interaction ($p = 0.04$). Of interest, FTO was associated with the variation of body composition in particular total body water ($p = 0.02$) concluding that whereas the Mediterranean diet is a good dietary treatment to reduce total body fat, data about FTO remain uncertain. Understanding the influence of FTO on body composition during dietary treatments is important to decide whether its effect has to be taken into consideration during both development of nutritional plans and patient monitoring.

Other dietary factors

Other dietary factors proposed to be useful as adjuvant for their potential anti-inflammatory effect (associated with antioxidant activity and inhibition of enzymes involved in eicosanoids production) are the polyphenols [108]. Studies showed that polyphenols intake can prevent CVD onset thanks to their antioxidant and antiatherosclerotic activity [109, 110]. It was recently demonstrated that supplementation with polyphenols from grape significantly reduced the serum levels of TMAO, an emerging risk factor for CVD [111, 112]. An interesting nutrigenetic association for the individual response to polyphenols intake has been attributed to the gene encoding for *PON1* enzyme (a glycoprotein able to protect lipoproteins from oxidation and consequently strongly associated with HDL cholesterol antioxidant and anti-inflammatory activity). SNPs in the *PON1* gene have been associated with susceptibility to CVD and atherosclerosis [113], but this association was interestingly linked to polyphenols and anthocyanins consumption [108]. In particular *PON1* variants (rs854549, rs854552, rs854571, and rs854572) could identify subjects who effectively take advantage from targeted polyphenols dietary intake in terms of CVD prevention.

Coffee, and in general caffeine, intake is another issue that is commonly linked to cardiovascular outcomes. Interestingly, an observational study reported that coffee intake is negatively associated with metabolic syndrome prevalence, waist circumference, blood pressure, HDL cholesterol, LDL cholesterol, and triglycerides levels in psoriatic patients [114], suggesting the potential protective role of moderate (2–3 cups per day) consumption of coffee, probably due to the high amount of polyphenols. However, considering that there is no completely clear epidemiological evidence about the link between habitual coffee intake and the development of hypertension [115], nutrigenetic interactions are proposed as potentially able to explain part of the interindividual variability in the cardiovascular effects of coffee drinking. Several polymorphisms located in genes regulating caffeine metabolism (i.e., *CYP1A2*) or encoding for adenosine and adrenergic receptors (i.e., *ADORA2A*, *ADRA1A*, *ADRA2B*, *ADRB1*, *ADRB2*, and *ADRB3*) have been suggested to explain these heterogeneous cardiovascular effects of coffee consumption. Slow metabolizers of caffeine according to *CYP1A2* genotype, in particular, displayed tachycardia, increased aortic stiffness, higher pulse wave velocity, vascular inflammation, and increased catecholamines after 3 h from caffeine consumption in comparison with the fast metabolizers [116]. Despite numerous studies investigating genotype mediated effects of caffeine on CVD risk, contrasting evidence emerged [117].

Limits and pitfalls of nutrigenetic approach to prevent CVDs

Several authors raised the question about the need for tailored nutrition in CVD prevention [118, 119]. Most of them concluded that, while it would be a promising field for the near future, there is a need for more evidence in our understanding of gene–nutrient interactions before it would be possible to translate these data into clinical practice [120]. Nevertheless, by now, it is impossible to ignore the potential implications of nutrigenetics on public health (including CVD prevention) in terms of (i) definition of personalized dietary requirement identification; (ii) identification of nutrient intake combinations ideal for the homeostasis of specific genomic profiles; (iii) better understanding of epidemiological data, clarifying the origin of the heterogeneous responses measured in populations after specific dietary intervention; and (iv) optimized intervention and prevention strategies [67].

As a matter of fact, despite a noteworthy body of scientific evidence on gene–diet interactions determining CVD phenotypes which clearly demonstrated that genetic influence on CVDs is mediated by diet, moving from bench to bed-side still actually represents a challenge for personalized nutrition. This is, at least in part, due to intrinsic limits of nutrigenetic studies (such as neglecting the possible overall interactions between numerous gene variants [121] with different nutritional interactions) and the lack of systematic review and meta-analysis of gene–diet interactions. These studies are mandatory to better estimate the effect size of gene–diet interactions and to identify the most predictive variants for which genotyping should be recommended. In this contest, Corella et al. [122] recently published a guide for upcoming studies and implementations necessary to overcome the current limits in nutrigenetics, while Grimaldi et al. proposed a guideline to evaluate the scientific evidence for genotype-based dietary advice in order to correctly introduce them into clinical practice [123].

Another aspect that could limit application of nutrigenetics is that the prevalence of the analyzed SNPs varies significantly among different ethnic groups and the association with the identified phenotype is not always confirmed in populations of different ethnicities. Furthermore, while communicating nutrigenetic data seems to promote motivation and adherence to diets [124], a recent systematic review demonstrated that to communicate the genetic risk of cardiometabolic disorders does not significantly impact motivation and actual engagement in preventative lifestyle modification and clinical outcome [125]. This suggests that the mediation of nutritionists and physicians is mandatory to correctly translate nutrigenetic information into clinical advice and to obtain real benefits for patients.

Conclusion

Undeniably, nutrigenetics is still in infancy with respect to research conducted on CVD prevention and therapy; nevertheless, the development of high-throughput (and cheaper) technologies and the increasing number of intervention studies including also nutrigenetic analysis have strongly contributed to produce consistent results [88, 126–129]. This promising landscape would be further enhanced by the co-application of other "omics" disciplines (i.e., epigenomics, nutrigenomics, metabolomics, lipidomics, transcriptomics, and proteomics). Dogan et al., for instance, recently demonstrated the ability of an integrated approach to successfully model symptomatic coronary heart disease status by integrating genetic, epigenetic and phenotype data from the Framingham Heart Study [126]. This inclusive approach is actually converting personalized nutrition and medicine into a reality, particularly in the field of CVD prevention in obesity.

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