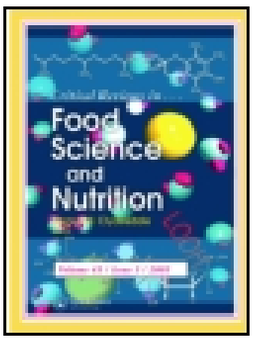

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The future of Nutrition: Nutrigenomics and Nutrigenetics in Obesity and Cardiovascular Diseases

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Abstract

Over time, the relationship between diet and health has aroused great interest, since nutrition can prevent and treat several diseases. It has been demonstrated that general recommendations on macronutrients and micronutrients do not affect to every individual in the same way because diet is an important environmental factor that interacts with genes. Thus, there is a growing necessity of improving a personalized nutrition to treat obesity and associated medical conditions, taking

into account the interactions between diet, genes and health. Therefore, the knowledge of the interactions between the genome and nutrients at the molecular level, has led to the advent of nutritional genomics, which involves the sciences of nutrigenomics and nutrigenetics. In this review, we will comprehensively analyze the role of the most important genes associated with two interrelated chronic medical conditions, such as obesity and cardiovascular diseases.

Keywords

gene, polimorphism, nutrigenomics, nutrigenetics, obesity, cardiovascular diseases.

ACCEPTED MANUSCRIPT

Abbreviations

ABI Ankle-brachial index

ACS Acute coronary syndrome

AMI Acute myocardial infarction

AGRP Agouti-related protein

BMI Body mass index

CAD Coronary artery disease

CBS Cystathionine beta synthase

CHD Coronary heart disease

CRP C reactive protein

CVDs Cardiovascular diseases

EI Energy intake

GWAS Genome-wide association studies

HCY Homocysteine

HDL high density lipoprotein

HGP Human genome project

LDL Low density lipoprotein

PUFAsPolyunsaturated fatty acids

SFA Saturated fatty acids

SNP Single nucleotide polymorphim

TNFα Tumour necrosis factor-alpha

TTE Total energy expenditure

WHO World health organization

VLDL Very-low density lipoprotein

Introduction

The word “nutrition” was not frequently used up to the second half of the 18th century, when the French Chemist Lavoisier established the scientific bases of the modern nutrition (Prentice, 1995). The WHO (World Health Organization) in 1948, defined the nutrition as “a set of processes by which living beings incorporate, modify and remove substances from outside" (Sadeghirad et al, 2016). Due to the key role of food in achieving and maintaining health, an intensive investigation was started about food and its effect on health (Narayanaswami and Dwoskin, 2016).

Genetics studies the phenomena of the inheritance and their variations (Ordovás & Corella, 2004). It is an area of great expansion with important economic, ethical and social implications. In 1990, two big events took place, beginning the genetic revolution: Firstly, the Human Genome

Project (HGP) was started and, secondly, for the first time, human cells received genes to modify their genetic inheritance and to treat certain diseases (Santos, 2004; Kussmann & Van Bladeren, 2004). In 2004, the almost complete determination of the human genome sequence marked a scientific milestone without precedents in the biology.

For decades, the knowledge of different inter-individual response to the same diet has been established. Although it is clear that both, nutrients and genes, play a distinct role in determining health, the complex interactions among genes, diet, and downstream networks are not well understood (Eaton et al, 2001). Different studies have classified individuals in normo-responders, hypo-responders or hyper-responders depending on their phenotypic response to the diet (Kolovou et al, 2016). The huge amount of discoveries about of the role of the human genome in the nutrition, led to create a new discipline: the Nutritional Genomic or Molecular Nutrition, promising a better treatment and disease prevention through more individualized diets (Mutch et al, 2005) (Figure 1). To analyze this new information, the “omics” sciences were utilized. These sciences, led by the “genomics” have subsequently resulted in the “transcriptomics,” “proteomics,” “metabolomics,” “microbiomics” and epigenetics, and all together establish the “nutrigenomics” and the ”nutrigenetics" (Ferguson et al, 2016). Whereas nutrigenomics studies the influence of the nutrients on gene expression, nutrigenetics studies the influence of the genetic variations in the body promoted by the nutrients (Figure 1).

At this point, it could be said that both, the genetic and the environment, participate in the phenotype of a certain individual, receiving quantitatively more importance one of them, according to the disease (Corella & Ordovás, 2005). Undoubtfully, among the environmental

factors, the diet is quantitatively the most important, since it is the one we are more exposed to and can be easily modified according to the necessities of each person (de Luis et al, 2016).

Indeed, nutrition has great importance in classic metabolic diseases, such as in galactosemia, phenylketonuria, congenital hyperhomocysteinemia, since a compatible diet (low diets in galactose, phenylalanine or rich diets in folic acid, respectively) can modify the phenotype that has been affected by alterations in one gene (Staubach et al, 2016). However, the challenge is to be able to treat also multifactorial diseases (when its expression is determined by a combination of several genes and another non-genetic factors) more complex and prevalent, such as, obesity, cardiovascular diseases (CVDs), cancer, diabetes, dementias, among others. It is widely known that chronic diseases are mainly caused by inadequate life style; nevertheless, nutrition itself does not avoid them, but may help to prevent and ameliorate them. The aim of this review is to comprehensively study and analyze the role of the most important genes associated with two of the most prevalent diseases in Western countries, obesity and CVDs.

Methods

Published data for this review were identified by search and selection database of MEDLINE, Google Scholar, PubMed, Elvesier, Scielo. Reference lists from relevant articles, reviews and books on the subject were obtained. A two-step approch was used. First, a search with the keywords: ‘'nutrition'’, ‘'nutrigenomics”, "nutrigenetics'’, ‘'obesity'’ and ‘'cardiovascular disease'’ was carried out. In this first selection, 68 articles were initially found. Secondly, the role of the genes and polymorphisms associated with obesity and cardiovascular diseases were evaluated, adding them to a second selection: ‘'FTO'’, ‘'INSIG2'’, ‘'MC4R'’, ‘'ApoA'’, “MTHFR”, “PPAR”,

"ApoE" and "LIPC." Bibliographies of all selected articles and review articles about nutrigenomics and/or nutrigenetics were also reviewed for other relevant articles.

Nutrigenomics and Nutrigenetics in Obesity

Obesity is a medical condition with a multifactorial origin resulting from an imbalance between the Energy Intake (EI) and the Total Energy Expenditure (TEE), associated with alterations of many metabolic pathways (Goni et al, 2016). This imbalance leads to an accumulation of excess body fat and manifests itself as a system dysfunction of weight control. Obesity has special importance since it can contribute to the appearance or development of other diseases (Martínez, 2014). It is considered the main risk factor for the development of diabetes type-2, since it is estimated that 61% of obese people will develop diabetes type 2 in their life (Lehnert et al, 2015). Furthermore, it represents the principal risk factor associated with cardiovascular mortality in the world (Lehnert et al, 2015).

Despite obesity is associated with an energy imbalance, it can also be linked to several metabolic and endocrine disorders. Indeed, although genetic factors are likely to set the stage for obesity; diet, exercise and lifestyle determine the magnitude of the problem (Loos & Bouchard, 2003). In other words, the susceptibility to obesity is partly determined by genetic factors, but an 'obesogenic' environment is typically necessary for its phenotypic expression. Thus, although new evidence of genetic influence and neuroendocrine imbalance appears every day; it is necessary to consider a holistic model in which biological and psychosocial factors interact in a complex form. So, the Nutrition Science has established the concept of 'gene-nutrient

interaction', being the gene expression a key factor influencing the obesity risk and development (Martínez, 2014).

Genes associated to obesity

Several genes and single nucleotide polymorphisms (SNPs) have been associated with obese phenotypes in both animal and human studies; some of them discovered using genome-wide association (GWAS) technology (Qi et al, 2014; Miae & Yangha, 2015). Indeed, several studies have found a relationship between genetics and a predisposition to obesity and their associated comorbidities. The role of some of these genes will be discussed thoroughly below.

FTO gene

One of the most important genes associated to obesity is the FTO gene (fat mass and obesity associated) located on chromosome 16 (Table 1). Several SNPs in the FTO gene have been suggested to be associated with increased body mass index (BMI), hip circumference, and weight (Scuteri et al, 2007). Although it has also been suggested that the risk alleles of adiposity of this gene predispose to diabetes mellitus, hypertension and cardiovascular events in high-risk populations, it was primarily associated with obesity and increased BMI in cross-sectional studies (Scuteri et al, 2007). A study performed in 6,148 individuals from a genetically isolated population of Sardinia tested 362,129 SNPs associated to obesity using GWAS technology. Initial analysis suggested that several SNPs in the FTO gene were associated with BMI, hip circumference and weight. In addition, within the FTO gene, the SNP rs9930506 was the variant showing more consistent associations with BMI, hip circumference and weight ($p<0.0001$ for all of them). It was observed that homozygotes for the rare "G" allele of this SNP (minor allele

frequency = 0.46) were 1.3 BMI units heavier than homozygotes for the common “A” allele (Scuteri et al, 2007).

Another cross-sectional study was performed in 129 patients with morbid obesity (IMC>40) analyzing the relationship of the rs9939609 FTO gene polymorphism on body weight, cardiovascular risk factors and serum adipokine levels (de Luis et al, 2012). Of these 129 patients, 41 had TT genotype, 55 had TA genotype and 33 had AA genotype. BMI, fat mass, weight, C reactive protein (CRP) and leptin levels were higher in mutant type group (A allele) than in the wild genotype group (TT). It was therefore determined that the FTO gene polymorphism rs9939609 was independently associated with weight, fat mass, CRP and leptin levels in morbid obese patients with the A allele (de Luis et al, 2012).

A very recent prospective study performed in a cohort of 357 Romanian obese children analyzed if there was any association between FTO gene variants rs9939609 and rs17817449 with anthropometric and metabolic biomarkers (fasting glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, triglycerides) and adipokines levels (adiponectin and leptin) (Duicu et al, 2016). Significant associations were found between FTO rs9939609 SNP and obesity. AA genotype carriers have more than two-fold higher risk for obesity compared with AT+TT genotype carriers. Risk allele carriers of rs17817449 SNP (GG) had also higher values of weight, body mass index, waist and hip circumference, total cholesterol, triglycerides, adiponectin, and fasting glucose. This study also established that combined variant genotypes (AA/GG) of FTO rs9939609/rs17817449, were strongly associated with several measures of adiposity (weight,

BMI, mid-upper arm circumference, tricipital skinfold thicknesses…) and were also significantly associated with total cholesterol, triglyceride, and LDL-cholesterol levels (Duicu et al, 2016).

Remarkably, recent large-scale analyses based on data from 177,330 adults (154,439 Whites, 5,776 African Americans and 17,115 Asians) from 40 studies were performed to examine the association between the FTO rs9939609 variant, dietary intake and BMI (Qi et al, 2014). The minor allele (A-allele) of the FTO rs9939609 variant was significantly associated with higher BMI in Whites, Asians and all participants combined, but no association was found in African American. In addition, this allele of the FTO variant showed a significant association with higher dietary protein intake that remained significant after adjustment for BMI. Furthermore, the combined effect of the polymorphism in the FTO gene, together with the genetic variant (SNP rs17782313) in the MC4R gene (melanocortin-4 receptor), another gene previously implicated in obesity and BMI, was associated with dietary intakes and BMI. As expected, the MC4R genetic variant was significantly associated with BMI; however, the effect size of the FTO variant on BMI was larger than that of the MC4R variant (Qi et al, 2014).

INSIG2 gene

Another important gene associated to obesity is the INSIG2 gene (insulin-induced gene 2), located on chromosome 2 (Table 1). A prospective study, performed in 1,058 students identified 3 polymorphisms in INSIG2 associated with overweight (BMI≥85% for age) and dyslipidaemia in children (rs12464355, rs17047757, rs7566605). A significant association between the rs12464355 SNP and elevated LDL levels were found in non-hispanic white children, being the G allele protective (lower LDL). Moreover, rs17047757 SNP was also significantly associated

with overweight. However, SNP rs7566605 was not associated with overweight or lipid levels (Kaulfers et al, 2015).

The impact of INSIG2 polymorphisms on obesity and overweight is controversial. In a recent study, no significant associations were found between the rs7566605 SNP of INSIG2 with obesity or other metabolic parameters in a cohort of 672 Malaysian individuals (Apalasamy et al, 2014). In addition, another study also analyzed the INSIG2 polymorphism rs7566605 in 124 unrelated morbidly obese patients (mean BMI = 50, range 40.1-77.1) and in 253 normal controls without a history of morbid obesity and found no association of this potential obesity risk allele and thus cannot confirm an association of the INSIG2 CC genotype with obesity.

Strikingly, INSIG2 polymorphism rs7566605 were not associated with obesity in these studies, but a large meta-analysis (34 studies, 74,345 individuals) revealed an increased obesity risk for rs7566605 minor allele homozygotes in general population studies (CC genotype) (Heid et al, 2009). These discrepancies increased with age-related studies showed that tests for rs7566605--age interaction were not significant for early childhood to middle age (4--40 years) (Liu et al, 2011; Fornage et al, 2010); however, a lower gain in weight-for-length was reported for CC genotype babies between birth and the age of 6 months (Wu et al, 2009) and, conversely, the risk of obesity increases rapidly with age and is elevated for ages >40 years (Malzahn et al, 2014). Furthermore, and for more complexity, the INSIG2 polymorphism rs7566605 was previously associated with the polymorphism rs2229616 in the melanocortin-4 receptor (MC4R), a gene that contributes to hormonal appetite control in response to the amount of adipose tissue (Friedman, 2004). The known functional rs2229616 SNP in MC4R (missense variant V103I) has

been previously associated with altered BMI (Young et al, 2007; Heid et al, 2008). Minor allele carriers (A) had lower BMI, lower risk of obesity (Young et al, 2007) and beneficially altered triglyceride and HDL cholesterol levels (Heid et al, 2008). Importantly, it was found that INSIG2 minor allele homozygotes (CC) accumulate a gain of BMI in the elderly but the presence of the MC4R protective genotype (GG) can intercept this increase. Hence, elderly INSIG2--MC4R CC-AA genotype subjects are particularly at risk of obesity. This also may explain previous INSIG2 main effect replication failures, suggesting that the proportion of younger and elderly subjects in a study can influence association outcome when not accounting for SNP--age interaction (Malzahn et al, 2014). Moreover, these studies demonstrate the complexity of genetics and the importance of other factors such as age in the expression of genes and in the final phenotype.

MC4R gene

The melanocortin-4 receptor (MC4R) is a part of the melanocortinergic pathway that regulates food intake and controls energy homeostasis. The most common polymorphism, the isoleucin rare variant (A allele) of the V103I polymorphism (rs2229616; G>A), with a frequency of 3--4%, was first described in 1997 (Gotoda et al, 1997). Recent functional studies have revealed that, compared to the wild-type receptor, the infrequent I103 allele is less responsive to agouti-related protein (AGRP) (Xiang et al, 2006). AGRP is an endogenous antagonist of the MC4R that stimulates energy intake and promotes weight gain (Ollmann et al, 1997; Schwartz et al, 2000; Bewick et al, 2005). Thus the V103I-mediated attenuation in MC4R activation by AGRP might lead to a relatively weaker orexigenic signal; in turn, this may result in a comparatively lower risk of obesity in human populations.

As far as we know, the first MC4R pooled-analysis was based on 3,631 cases and 4,082 controls, and suggested that individuals with the I103 allele might have a 31% reduced risk of obesity; however, this association had only marginal statistical significance (Geller et al, 2004). Later, the KORA study analyzed the association of this polymorphism with features of the metabolic syndrome, such as waist circumference, glysosylated hemoglobin, HDL-c and blood pressure in 7,888 individuals (Heid et al, 2008). The MC4R V103I polymorphism was significantly associated with a decrease of waist circumference ($p = 0.02$) and glysosylated hemoglobin ($p = 0.04$), whereas a trend towards HDL-c increase ($p = 0.056$) was observed. Blood pressure was the only feature of metabolic syndrome without V103I polymorphism association. Remarkably, the possibilities of having three or more components of the metabolic syndrome were substantially reduced among carriers of MC4R 103I (odds ratio = 0.46, $p = 0.003$).

Another meta-analysis involving 29,563 individuals was performed to assess the association between the V103I polymorphism in the MC4R gene and obesity (Young et al, 2007). This study confirmed that individuals carrying the isoleucine allele had an 18% ($p = 0.015$) lower risk of obesity compared with noncarriers without heterogeneity among studies and no apparent publication bias. The limitation of this study is that of the 22 datasets analyzed, 21 represented Caucasian populations and only 1 contained data from Black Americans.

More recently, an interesting study analyzed the association of the V103I polymorphism in the MC4R gene from two different points of view. A Chinese case-control study with 2,012 children of two independent study groups from China, and two meta-analyses; one in 3,526 individuals of six East Asian studies and the other one in 55,195 individuals of these 6 East Asian studies

combined with 31 studies of other ethnic groups (28 studies of white origin, two studies of African Americans and one Turkish study) (Wang et al, 2010). Regarding the case-control study in two independent study groups of Chinese children, the frequency of I103 carriers was higher in the non-obese group than in obese individuals in both studies. Although the frequency difference was not statistically significant, the trend was consistent with the previous studies in other populations. Additionally, in the meta-analysis of 3,526 individuals from six East Asian studies, I103 carriers had a 31% lower risk for obesity ($p = 0.02$). Subsequently, an updated meta-analysis in 55,195 individuals of 37 studies, including 19,822 obese cases and 35,373 non-obese controls was carried out and found that individuals with the I103 allele have a 21% reduced risk to develop obesity. Hence, all these observations further confirmed that the presence of the isoleucine in the rs2229616 polymorphism was associated with a reduced risk of obesity.

APO-A family gene

Near the end of the seventies, a family of Apolipoproteins was discovered in humans, the Apolipoprotein-A (APO-A). The gene coding for this APO-A is tandemly organized within a 15-kilobase (kb) DNA segment on the long arm of human chromosome 11 (Antonarakis et al, 1988). APO-A was mainly associated with triglyceride-rich lipoproteins (Table 1). The most important allele APO-A gene variations are: APO-A1, APO-A2, APO-A4 and APO-A5, being one of the most studied genetic variables because of its relevance in the field of nutrition and CVDs (Antonarakis et al, 1988). Moreover, in white and Asian populations, variation in this gene is the major determinant of the plasma concentrations of the atherogenic lipoprotein-A, which varies enormously among individuals and considerably across populations.

One study examined the relationship between APO-A4 gene T347S polymorphism with obesity measures and serum lipids in Turkish adults. Randomly selected sample of 1,554 adults (754 men, mean age 50.4 ± 11.9 years and 800 women, mean age 49.6 ± 11.8 years) were included in the study. It was observed that the APO-A4 S347 allele predisposes to obesity and high waist circumference in Turkish postmenopausal women (Guclu-Geyik et al, 2012).

More recently, another study analyzed the interaction of a high fat diet with the APO-A2 (rs3813627 and rs5082) and APO-A5 (rs662799 and rs3135506) polymorphisms and their relationship with obesity and dyslipidemia in 200 young subjects aged 18 to 25 years (100 normal-weight and 100 obese subjects). Dietary fat intake was measured using the frequency food consumption questionnaire. The analysis of the clinical, biochemical and nutritional characteristics by genotypes in all subjects showed that the APOA2 -265 T/T genotype carriers had a higher intake of polyunsaturated fatty acids ($p = 0.02$) than the T/C + C/C carriers (rs5082 polymorphism). Furthermore, it was found that the carriers of the T/C + C/C genotypes for the APO-A5 -1131 T/C polymorphism (rs662799) had decreased levels of HDL-cholesterol ($p = 0.02$) and an increased intake of polyunsaturated fatty acids ($p = 0.037$) compared with the T/T genotype. Moreover, a significant association between the presence of the APO-A5 56 G/G genotype (rs3135506 polymorphism) with high saturated fatty acid consumption and with total fat consumption was found, thus increasing the risk of obesity (Domínguez-Reyes et al, 2015). This study showed that polymorphisms in APO-A genes were associated with different lipid intake and, therefore with risk of obesity.

On the other hand, a cross-sectional study, with a mean follow-up of 20 years, and case-control analyses was undertaken in 3 independent populations (Corella et al, 2009). This study was carried out in 3,462 individuals: The Framingham Study (unrelated non-Hispanic Whites (716 men and 738 women), The Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) (514 men and 564 women) of European ancestry) and Boston-Puerto Rican study (263 men and 667 women Hispanics of Caribbean origin). The interaction between the functional APOA2 −265T>C polymorphism (rs5082), food intake and BMI in independent populations was analyzed to replicate findings and to increase their evidence level. It was observed for the first time that when saturated fat intake is low, the APOA2 −265T>C SNP does not affect BMI; however, when saturated fat intake is high (high SATFAT), this SNP was strongly associated with BMI and obesity. In addition, the magnitude of the difference in BMI between the individuals with the CC and TT+TC genotypes differed, being the CC genotype significantly associated with higher obesity prevalence in all populations only in the high-SATFAT stratum. For the first time, a gene-diet interaction influencing BMI and obesity was strongly and consistently replicated in three independent populations (Corella et al, 2009). It is noteworthy that the APO-A2 −265T>C polymorphism can be considered as a thrifty genotype, as depending on the presence of an “obesogenic” (high-SATFAT diet) or “restrictive” (low-SATFAT diet) environment, the phenotypic expression is different.

Nutrigenomics and Nutrigenetics in CVDs

The WHO defines cardiovascular diseases (CVDs) as ‘'Diseases caused by disorders of the heart and blood vessels, and includes coronary heart disease (heart attacks), cerebrovascular disease

(stroke), raised blood pressure (hypertension), peripheral artery disease, rheumatic heart disease, congenital heart disease and heart failure''. They are the first cause of morbidity and mortality in the 21st century and according to forecasts, the situation will not change in the next decades (Mozaffarian et al, 2016). This disease might be prevented with a healthy lifestyle, making possible, in long term, to diminish their incidence in general population. Indeed, diet is a very important factor, since the great majority of the chronic diseases are preventable with hygienic and dietetic measures.

Over the years, many epidemiological and interventional studies have allowed us to characterize factors associated with an increased risk of CVDs including modifiable and non-modifiable risk factors. Regarding the modifiable dietary factors in CVDs, it is widely known that certain foods such as almonds or walnuts can reduce oxidation biomarkers related to cardiovascular risk and modify lipid profile in predisposed individuals; whereas fruits or vegetables decrease the risk of CVDs (Nishi et al, 2014; Wang et al, 2014). In fact, in subjects with high cardiovascular risk, a Mediterranean diet (characteristic of Mediterranean countries and declared Intangible Cultural Heritage of Humanity supplemented with extra-virgin olive oil or nuts) reduced the incidence of major cardiovascular events (Estruch et al, 2013).

Despite all these advances, mechanisms that underlie individual differences in the presentation and pathophysiological features of CVDs are poorly understood. Genetics has a very important role in CVDs, since a large number of genes and their variants may influence the CVD risk by different routes. Genetic variations interact with the environment and specific dietary intake can influence the overall risk of CVDs. With adequate information on the interaction between

specific genetic polymorphisms, diet and CVD risk, it may be possible to provide individuals dietary guidance tailored according to their genotype, increasing life expectancy and maintaining health and wellness (Juma et al, 2014).

Genes associated to CVDs

PREDIMED trial, "Primary prevention of cardiovascular disease with Mediterranean diets", showed that a Mediterranean diet is beneficial against the incidence of several major chronic diseases in subjects at high cardiovascular risk, particularly when improved with consumption of extra virgin olive oil (Estruch et al, 2013). However, it has been reported that these recommendations cannot be generalized, since each person responds differently to diet, being the interaction gene-nutrient in the spotlight. Below, we will analyze the role of different genes and polymorphisms in CVDs (Table 2).

MTHFR gene

The gen of the 5-10-Methylene tetrahydrofolate reductase (MTHFR) is located on the short arm of chromosome 1 and catalyzes the reduction of 5,10 methylene tetrahydrofolate (THF) to 5-methyltetrahydrofolate (primary form of serum folate, substrate for homo-cysteine remethylation to methionine). It encodes a protein of 77 KDa, which is a key enzyme in folate and homocysteine metabolism (Chen et al, 2016). A decreased in the activity of this enzyme causes an increase in homocysteine (HCY) plasma concentration (amino acid with atherogenic and prothrombotic properties) with the consequent increased risk of venous or arterial thrombosis and therefore cardiovascular risk (Chen et al, 2016).

The most common MTHFR polymorphism is caused by an impaired substitution of cytosine by thymine in the base 677 causing a substitution of valine for alanine at amino acid 222 of the enzyme (rs1801133) (Table 2). The TT genotype shows increased thermolability of the enzyme, associated with a lower activity and an increase in plasma homocysteine concentration. One recent study analyzed the correlation between serum HCY levels, 677C/T MTHFR gene polymorphism and coronary heart disease (CHD) (Chen et al, 2016). The study was performed in 208 CHD patients and in an additional 200 healthy volunteers as the control group. Compared to those in the control group, the serum HCY levels in the CHD patients were significantly higher. Moreover, the proportion of individuals with the heterozygous MTHFR CT genotype and homozygous mutant TT genotype among CHD patients was significantly higher than that in the control group. Furthermore, in the acute coronary syndrome (ACS) subgroup, the proportion of those with the CT and TT genotypes was significantly higher than that of the stable CHD subgroup. These observations clearly suggest that serum HCY levels and MTHFR C677T genotypes are associated with CHD and ACS (Chen et al, 2016).

Additionally to MTHFR, Methionine synthase (MTR) is also known to regulate the homocysteine remethylation reaction and promotes higher homocysteine levels, significantly associated with diverse cardiovascular phenotypes. A novel case control study enrolled a total of 435 individuals (195 CVD patients and 240 controls) and analyzed the above mentioned MTHFR C677T and the MTR A2756G gene polymorphisms (Raina et al, 2016). The evaluation of genetic association showed that, MTHFR 677C>T (OR: 8.89, 95% CI: 2.01-39.40) and MTR 2756A>G polymorphisms were significantly associated with higher risk of CVDs (OR: 1.48, 95% CI: 1.09-2.00) (Raina et al, 2016).

More recently, the role of several polymorphisms in homocysteine pathway genes in 254 CAD patients and 250 controls were analyzed together with homocysteine, folate and vitamin B12 plasma levels (Masud & Baqai, 2017). Two MTHFR polymorphisms (rs1801133, rs1801131), one MTR polymorphism (rs1805087), one paroxanse-1 (PON-1) polymorphism (rs662), and one cystathionine beta synthase (CBS) polymorphism (rs5742905) were investigated. Logistic regression analysis (adjusted) revealed that the presence of the two analyzed MTHFR polymorphisms (rs1801133, rs1801131) and the MTR polymorphism (rs1805087), along with homocysteine levels conferred higher risk for CAD. These results confirm previous studies with the same polymorphisms in a smaller population (Masud & Qureshi, 2011). Logistic regression, after adjusting for covariates, demonstrated significant associations of MTHFR polymorphism (rs1801133) and MTR polymorphism (rs1805087) with CAD. All these observations highlight the importance of several polymorphisms in homocysteine pathway genes associated with higher levels of HCY and a predisposition to suffer from different CVDs.

On the other hand, polymorphisms in homocysteine pathway genes have been recently associated with type 2 diabetes mellitus (Fekih-Mrissa et al., 2017) and hypertension (Li et al., 2017). In both studies, it was shown that the presence of several polymorphisms was not significantly associated with diabetes or hypertension; however, hyperhomocysteinemia was observed in patients when compared with controls. These results guarantee further studies in larger populations to confirm the role of both, polymorphisms in genes associated with homocysteine metabolism and high homocysteine blood levels in these diseases related with vascular complications.

PPAR gene

Other relevant genes that may explain the interaction of nutrigenomics and nutrigenetics with CVDs are the PPARs family (peroxisome proliferator-activated receptor) (Table 2). PPARs are ligand-regulated transcription factors that control gene expression by binding to specific response elements (PPREs) within promoters (Gearing et al, 1994). These metabolites have emerged as key regulators of gene-diet interaction, since they are involved in the regulation of glucose and lipid metabolism, adipocyte differentiation and inflammatory response. The natural ligands of PPARs are fatty acids, preferably PUFAs (polyunsaturated fatty acids) and their metabolites. The most important form associated with CVDs is the PPAR-γ2 (Peroxisome proliferator-activated receptor gamma-2), located in chromosome 3p25, mainly expressed in adipose tissue and involved in adipocyte differentiation and in fat accumulation (Latruffe et al, 1997).

One of the most studied polymorphisms in the PPAR-γ2 gene is the polymorphism rs1801282 that promotes the Pro12Ala substitution. One study analyzed the effects of a 2-year nutritional intervention with Mediterranean-style diets on adiposity in high-cardiovascular risk patients depending on the Pro12Ala polymorphism of the PPAR-γ2 gene (Razquin et al, 2009). It was a randomized trial performed in 774 high-risk subjects aged 55--80 years with a mean follow-up of 2 years. In this study there were three nutritional intervention groups: two of them of a Mediterranean-style diet and a third control group advised to follow a conventional low-fat diet. The results showed that carriers of the 12Ala allele allocated into the control group (conventional low-fat diet) had a statistically significant higher change in waist circumference compared with

wild-type subjects after 2 years of nutritional intervention. This adverse effect was not observed among 12Ala carriers allocated to both Mediterranean diet groups. It could be hypothesized that the Mediterranean diet seems to be able to reduce waist circumference in a high-cardiovascular risk population, reversing the negative effect that the 12Ala allele carriers of the PPAR-γ2 gene appeared to have (Razquin et al, 2009). More recent studies have also described this deleterious effect of the 12Ala carriers in subjects at cardiometabolic risk (Alsaleh et al, 2011; Alsaleh et al, 2012); however, the most striking effect of this polymorphism was recently discovered as this polymorphism had been also associated with longer lifespan (García-Calzón et al, 2015). In a total of 521 subjects (55-80 years), 12Ala carriers showed lower telomere shortening after 5 years compared with the Pro/Pro genotype ($p = 0.031$). Interestingly, this association was modulated by the Mediterranean Diet, as those Ala carriers who reported better conformity to it exhibited increased telomere length ($p<0.001$). Moreover, a decrease in carbohydrates consumption and an increase in mono- and polyunsaturated fatty acids were significantly associated with a telomere lengthening in the Ala carriers compared with the Pro/Pro subjects (p for interaction <0.001) (García-Calzón et al, 2015). These observations highlight the impact of this polymorphism, not only in the regulation of glucose and lipid metabolism, but also in the maintenance of gene telomeres integrity.

APO-A Family Gene

The APO-A family gene, as mentioned above, encodes key regulators of plasma lipids. In fact, a retrospective analysis performed in 627 subjects assessed the effects of a polymorphism in APOA5 (-1131T>C) (rs662799), in terms of its frequency among three dyslipidemic populations

and a control population, differences of allele frequency across available ethnic groups, and associations with specific lipoprotein triglycerides and cholesterol compartments (Aouizerat et al, 2003) (Table 2). Importantly, it was observed an elevation in the frequency of the rare C allele in a Chinese population ($p = 0.0002$) compared with Hispanic and European populations. Moreover, linear regression models predicted that the rare C allele elevates plasma triglycerides by 21 mg/dl, VLDL cholesterol by 8 mg/dl, and reduces HDL cholesterol by 2 mg/dl, concluding that APOA5 is an important determinant of plasma triglycerides and lipoprotein cholesterol, and is potentially a risk factor for CVD (Aouizerat et al, 2003). This heterogeneity in the frequency of APOA5 polymorphism across ethnic groups maybe the explanation about the lack of association as a risk factor within European populations. Thus, further investigations in more homogeneous and larger population samples are required.

Interestingly, the association of -1131T>C of APOA5 with elevated serum triglycerides and lower HDL cholesterol was also reported in a Japanese study (Endo et al, 2002). The frequency of this nucleotide polymorphism and its effect on hypertriglyceridemia were analyzed in 522 schoolchildren, observing that the presence of the rare C allele was significantly associated with higher serum triglycerides. In addition, children with the C allele had more than 2-fold increased risk for hypertriglyceridemia than the T allele carriers (Endo et al, 2002). This suggests that the role of APOA5 in lipid metabolism has a significant impact on coronary disease and warrants further investigation.

It is widely known the benefit of PUFAs (polyunsaturated fatty acids) in CVDs (Tortosa-Caparrós et al, 2016). The effect of PUFA intake on HDL-c concentrations is mainly modulated

by the APOA1 (main apolipoprotein of HDL). In the Framingham Offspring Study (755 men and 822 women), a significant interaction between the polymorphism -75G>A in the APOA1 gene (rs 670) and PUFA intake was observed in women (Ordovás et al, 2002). When PUFA intake was <4% of energy, the most common G allele subjects had approximately 14% higher HDL-c concentrations than did carriers of the A allele ($p<0.05$). Conversely, when PUFA intake was >8%, HDL-c concentrations in carriers of the A allele were 13% higher than those of G/G subjects ($p<0.05$). However, PUFA intake had no significant effect on either HDL cholesterol or ApoA1 concentrations in men. Thus, a triple significant interaction including gene, diet and gender was observed to be associated with the APOA1 -75G>A polymorphism. Thus, in women carriers of the A allele, higher PUFAs intake were associated with higher HDL-c concentrations, whereas the opposite effect was observed in G/G women (Ordovás et al, 2002).

All these data point that the analysis of APO-A variations for early detection, diagnosis, and treatment of genetically determined CVD could have a significant clinical impact. Perhaps, pharmacological modulation of the levels of these proteins in human patients could reduce VLDL and triglyceride levels, potentially elevating HDL-c. Such alterations would ameliorate the atherogenic profile, thus reducing the risk of CVDs.

APO-E Family Gene

It is synthesized by a gene found on chromosome 19 and is associated with a number of plasma proteins: very-low density lipoprotein (VLDL), low density lipoprotein (LDL), high density lipoprotein (HDL), chylomicrons, or chylomicron remnants, playing a crucial role in lipid metabolism (Singh et al, 2006). This gene has common variations (SNPs) that result in amino

acid changes in the protein at positions 112 and 158. Based on these changes, the three most common alleles of APO-E gene are ε2, ε3 and ε4, producing the three isoforms of protein APO-E2, APO-E3 and APO-E4. These three alleles give rise to three homozygous ε2/2, ε3/3 and ε4/4 and three heterozygous genotypes ε3/2, ε4/3 and ε4/2 (Mahley et al, 1999). The normal genotype is ε3/ ε3 with a frequency of 77%. The study of APO-E allelic variations in a comprehensive manner has served to demonstrate the association of different APO-E phenotypes with lipid disorders (Ghiselli et al, 1982). In fact, LDL-c levels are higher in ε4 individuals, intermediate in those with the ε3 isoform and lower in the ε2, thus supporting the hypothesis of the protective role of the APO-E2 isoform. Importantly, more than 15% of the variation in total plasma and LDL cholesterol levels may be attributed to this single gene locus showing a perfect correlation between APO-E genotypes and levels of total cholesterol and LDL-c.

One study in a Turkish population showed an increased CVD risk in coronary artery disease (CAD) patient carriers of the allele ε4, independently of their lipid levels (Attila et al, 2001). This study was performed in 199 subjects (114 male and 55 female) and plasma lipid levels and other risk factors were determined in all subjects. It was observed that the frequency of the ε4 allele was significantly higher in CAD patients, thus, concluding that APO-E4 polymorphism was associated with the development of CAD in Southern Turkey (Table 2).

Another study examined the effect of a quercetin supplementation (150 mg/d) on blood pressure, lipid metabolism, markers of oxidative stress, inflammation, and body composition in a high-risk population of 93 overweight-obese volunteers aged 25--65 with metabolic syndrome in relation to APO-E genotype (subgroups APO-E3 and APO-E4) (Egert et al, 2010). It should be noted that

the quercetin is a natural existing polyphenol compound, a plant-derived aglycone form of flavonoid glycosides and has shown anticancer capacity for liver, breast, nasopharyngeal and prostate carcinoma but has not been clinically approved yet (Su et al, 2016). Quercetin supplementation was associated with a significant reduction in serum HDL in APO-E4 subgroup but not in APO-E3 one. Moreover, it was found a significant decrease in systolic blood pressure, oxidized LDL levels and serum TNFα (Tumour Necrosis Factor alpha) in APOE3 individuals after quercetin supplementation. All these data indicate that the APO-E genotype may be an important determinant of the responsiveness to daily quercetin treatment in human intervention studies (Egert et al, 2010).

More recently, the risk of acute myocardial infarction (AMI) was associated with APO-E genotype depending on saturated fatty acids (SFA) intake. APO-E3 and APO-E4 genotypes were significantly associated with a high risk of AMI when a high consumption of SFA (>10%) was observed compared with APO-E2 carriers (Yang et al, 2007). The effect of APO-E polymorphisms and risk of AMI was analyzed in 1,927 case subjects and 1,927 population-based control subjects. A significant gene-diet interaction ($p = 0.0157$) was observed between APO-E3 and APO-E4 variants and AMI in the presence of high saturated fat; whereas this association was not found in the APO-E2 variant, thus supporting the hypothesis of the protective role of the APO-E2 isoform.

A recent meta-analysis based on 14 published studies including 5,746 CHD cases and 19,120 controls clearly clarified the relationship of APO-E polymorphism with CHD risk (Zhang et al, 2015). This analysis showed that carriers of APO-E2 allele decreased risk for CHD when

compared with those carrying ε3 allele ($p<0.001$), especially in Caucasian population. In addition, those with ε4 allele had a significant increased risk for CHD ($p<0.001$), especially in Mongoloid population. Taken together, this meta-analysis supported a genetic association between APO-E gene and CHD, reporting that ε4 increased the risk of CHD, whereas ε2 decreased it, confirming previous results.

LIPC Gene

The LIPC gene (hepatic lipase), located on the long arm of chromosome 15, is an important determinant of plasma HDL concentration and LDL subclass distribution and may, therefore, influence susceptibility to CAD (Table 2). Moreover, it would account for over 50% of HDL-c genetic variability in humans (Knoblauch et al, 2004). Most of it depends on a common polymorphism of the LIPC promoter, the -514C>T (rs1800588). The variant allele (T) confers a decreased expression and activity of LIPC.

An interesting study examined the relationship between LIPC polymorphism and CAD by genotyping rs1800588 in the LIPC promoter in a case-control study (-514C>T polymorphism) (Verdier et al, 2013). It was also investigated the relationship between this polymorphism and the ankle-brachial index (ABI), which is predictive of atherosclerosis progression and complications in patients at high cardiovascular risk. This study was performed in 557 men aged 45-74 with stable CAD and 560 paired controls genotyped for rs1800588 polymorphism. Importantly, CAD cases showed a higher T-allele frequency than controls. In addition, TT-homozygosity was significantly associated with an increase of 6.4-fold of CAD risk when triglycerides were below 1.5 g/L, but no association was found at higher triglyceride levels. Furthermore, association of

the T-allele with pejorative ABI (<0.90) was significant for heterozygotes and for all T-carriers. To sum up, the -514T LIPC allele was associated with CAD under normotriglyceridemic conditions and constitutes an independent factor of deletereous ABI in coronary patients (Verdier et al, 2013).

However, a meta-analysis of 25 publications on this SNP, comprising over 24,000 individuals, and its relationship with total cholesterol, LDL-c, HDL-c, triglycerides, and LIPC activity partially confirmed these results (Isaacs et al, 2004). Significant decreases were observed in LIPC activity for both the CT and TT genotypes compared with the CC genotype ($p<0.001$); whereas mean plasma HDL-c levels in the CT and in the TT carriers group were increased compared with the CC group ($p<0.001$).

Due to these controversial results, novel studies have been performed. In a recent case-controlled study with 850 obese children and 2119 controls, the association between LIPC -514C>T polymorphism, obesity and plasma lipid profile in Chinese children and adolescents were evaluated (Wang et al, 2015). A significant association between the polymorphism (T allele presence) and obesity was observed in boys ($p = 0.042$), but not in girls. Moreover, a significant relationship of the polymorphism with total cholesterol and HDL-c independent of obesity in boys was observed. Furthermore, the T allele carriers had higher levels of LDL-c in obese boys, and also an increase in triglyceride, total cholesterol and LDL-c in non-obese girls (all $p<0.05$).

A recent analysis evaluated the role of the -514C>T (rs1800588) gene polymorphism of the LIPC in a group of 1,468 subjects belonging to the Genetics of Atherosclerotic Disease (GEA) Mexican Study (Posadas-Sánchez et al, 2015). The TT genotype was significantly associated

with increased levels of triglycerides, apolipoprotein A1 and triglycerides/HDL-c index, among others. On the other hand, the risk analysis showed that under a dominant model, the polymorphism was associated with increased risk of type 2 diabetes, hypertriglyceridemia and coronary artery calcification, thus suggesting that the LIPC -514C>T polymorphism was associated with cardiometabolic parameters and cardiovascular risk factors being a potential marker for subclinical atherosclerosis.

All these observations, despite several controversial data, confirm the influence of the rs1800588 LIPC polymorphism in a deleterious serum lipid profile and in several cardiovascular risk factors, such as, obesity, type 2 diabetes mellitus, atherosclerosis and coronary artery calcification, among others.

Clinical implications and future directions of nutrigenomics and nutrigenetics

Whereas nutrigenomics and nutrigenetics cannot be rigorously applied to obesity and cardiovascular prevention and treatment at this time, important results are being generated that will serve as the basis to increase the consistency of future research. At that point, nutrigenomics and nutrigenetics will become a reality in dietary personalization, in cardiovascular medicine, and subsequently in optimizing CVD treatment and prevention (Corella & Ordovás, 2009). In the near future, through the application of nutrigenomics and nutrigenetics, individuals might be able to get its complete genetic information and therefore, the knowledge of their genetic predisposition to obesity and chronic diseases, such as CVDs.

Conclusions

Undoubtedly, nutrigenomics and nutrigenetics are growing sciences, evolving many areas of investigation such as ethics, medicine, genetics and nutrition. The vast array of data collected from GWAS must now be empowered and explored through more complex interaction studies using standardized methods, larger sample sizes, population studies with appropriate experimental designs, clinical trials, and product-specific trials in subjects selected for specific genetic variants. The goal is to obtain more efficient individual dietary intervention strategies aimed at preventing disease, improving quality of life and achieving healthy aging. Thus, it is expected to change some of the nutritional criteria used today opening the way to the personalized nutritional recommendations. Indeed, from the Public Health point of view, the understanding of really important gene-diet modulations could help to profile the general dietary recommendations for each population.

Disclosure of interests

The authors report no conflicts of interest.

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Table 1. Summary of studies associating gene polymorphisms with obesity.

Gene	Polymorphism	Main Findings	References
FTO Gene	rs9930506	Homozygotes for the rare "G" allele were 1.3 BMI units heavier than homozygotes for the common "A" allele.	Scuteri et al, 2007
	rs9939609	BMI, fat mass, weight, C reactive protein (CRP) and leptin levels were higher in mutant type group (A allele) than in the wild genotype group (TT)	De Luis et al, 2012
		AA genotype carriers have more than two-fold higher risk for obesity compared with AT+TT genotype carriers.	Duico et al, 2016
		A allele was associated with higher BMI and higher protein intake in a meta-analysis with 177,300 individuals	Qibin et al, 2016
	rs17817449	Risk allele carriers (GG) had higher weight, BMI, waist and hip circumference, total cholesterol, triglycerides, adiponectin, and fasting glucose.	Duico et al, 2016
INSIG2 Gene	rs12464355	Elevated LDL levels were found in non-hispanic white children, being the G allele protective.	Kaulfers et al, 2015
	rs17047757	The polymorphism was significantly associated with overweight.	Kaulfers et al, 2015
	rs7566605	CC genotype was associated with increased obesity risk in a meta-analysis with 74,345 individuals	Heid et al, 2009
		Increased obesity risk for minor allele homozygotes (CC). This polymorphism seems to be related to gain of BMI in the elderly.	Malzahn et al, 2014
MC4R gene	rs2229616	I103 allele had an 18% lower risk of obesity in a meta-analysis involving 29,563 individuals	Young et al, 2007
		I103 was significantly associated with features of metabolic syndrome in 7,888 individuals	Heid et al, 2008
		Individuals with I103 allele have a 31% reduced risk of obesity	Geller et al, 2004
		I103 was associated with a reduced risk of obesity in a case control study and two meta-analyses	Wang et al, 2010
APO-A Gene	rs675	APO-A4 S347 allele predisposes to obesity and high waist circumference in Turkish postmenopausal women.	Gluclu-Geyik et al, 2012
	rs5082	APOA2 -265 T/T genotype carriers had a higher intake of PUFAs than the T/C + C/C carriers.	Domínguez-Reyes et al, 2015

	rs662799	T/C + C/C genotypes (APO-A5 -1131 T/C) had lower levels of HDL and an increased intake of PUFAs compared with the T/T genotype.	Domínguez-Reyes et al, 2015
	rs3135506	APO-A5 56 G/G genotype was associated with high saturated fatty acid and with total fat consumption, thus increasing the risk of obesity.	Domínguez-Reyes et al, 2015
	rs5082	When saturated fat intake is low, the APOA2 −265T>C SNP does not affect BMI; however, when saturated fat intake is high, the CC genotype is strongly associated with BMI and obesity.	Corella et al, 2009

Abbreviations: APO-A: Apolipoprotein-A; BMI: Body mass index; CRP: C-reactive protein; FTO: Fat mass and obesity associated; HDL: High-density lipoprotein; INSIG2: Insulin-induced gene 2; LDL: Low-density lipoprotein; MC4R: Melanocortin-4 receptor; PUFAs: Polyunsaturated fatty acids.

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Table 2. Summary of studies associating gene polymorphisms with CVDs.

Gene	Polymorphism	Main Findings	References
MTHFR Gene	rs1801133	Serum HCY levels in the CHD patients were higher than in controls. Frequency of the T allele among CHD and ACS patients was significantly higher than that in controls.	Chen et al, 2016
		The T allele was significantly associated with higher risk of CVDs	Raina et al, 2016
PPAR gene	rs1801282	Carriers of the 12Ala allocated into the control group had a significant higher change in waist circumference compared with wild-type subjects.	Razquin et al, 2009
		12Ala carriers showed lower telomere shortening compared with the Pro/Pro genotype. Mediterranean Diet, low carbohydrates and high PUFAs in Ala carriers exhibited increased telomere length.	García Calzón et al, 2015
APO-A Gene	rs662799	The rare C allele elevated plasma triglycerides, VLDL and reduced HDL	Aouizerat et al, 2003
		The rare C allele was associated with higher serum triglycerides and with a 2-fold increased risk for hypertriglyceridemia	Endo et al, 2002
	rs 670	In women carriers of the rare A allele, higher PUFA intakes was associated with higher HDL, whereas the opposite effect was observed in G/G women	Ordovás et al, 2002
APO-E Gene	APO E ε2/ε3/ε4 polymorphism	Increased CVD risk in CAD patients' carriers of the allele ε4, independently of their lipid levels.	Attila et al, 2001
	APO E ε2/ε3/ε4 polymorphism	Quercetin supplementation was associated with a reduction in serum HDL in APO-E4 subgroup but not in APO-E3 one. A decrease in systolic blood pressure and oxidized LDL levels in APO-E3 was found	Egert et al, 2010
	APO E ε2/ε3/ε4 polymorphism	APO-E3 and APO-E4 genotypes were significantly associated with a high risk of AMI when a high consumption of SFA was observed compared with APO-E2 carriers	Yang et al, 2007
	APO E ε2/ε3/ε4 polymorphism	ε4 increased the risk of CHD, whereas ε2 decreased it	Zhang et al, 2015
	rs1800588	The -514T LIPC allele was associated with CAD under normotriglyceridemic conditions and constitutes an independent factor of deletereous ABI in coronary patients	Verdier et al, 2013

LIPC Gene		The T allele carriers have higher levels of LDL in obese boys, and triglyceride, total cholesterol and LDL in non-obese girls.	Wang et al, 2015
		TT genotype was associated with increased levels of triglycerides, apolipoprotein A1, triglycerides/HDL index and atherosclerosis.	Posadas-Sánchez et al, 2015

Abbreviations: ACS: Acute coronary syndrome; AMI: Acute myocardial infarction; APO: Apolipoprotein; BMI: Body mass index; CAD: Coronary artery disease; CHD: Coronary heart disease; HCY: Homocysteine; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; LIPC: Hepatic lipase; MTHFR: 5-10-Methylene tetrahydrofolate reductase; PPAR: Peroxisome proliferator-activated receptor; PUFAs: Polyunsaturated fatty acids; SFA: Saturated fatty acids.

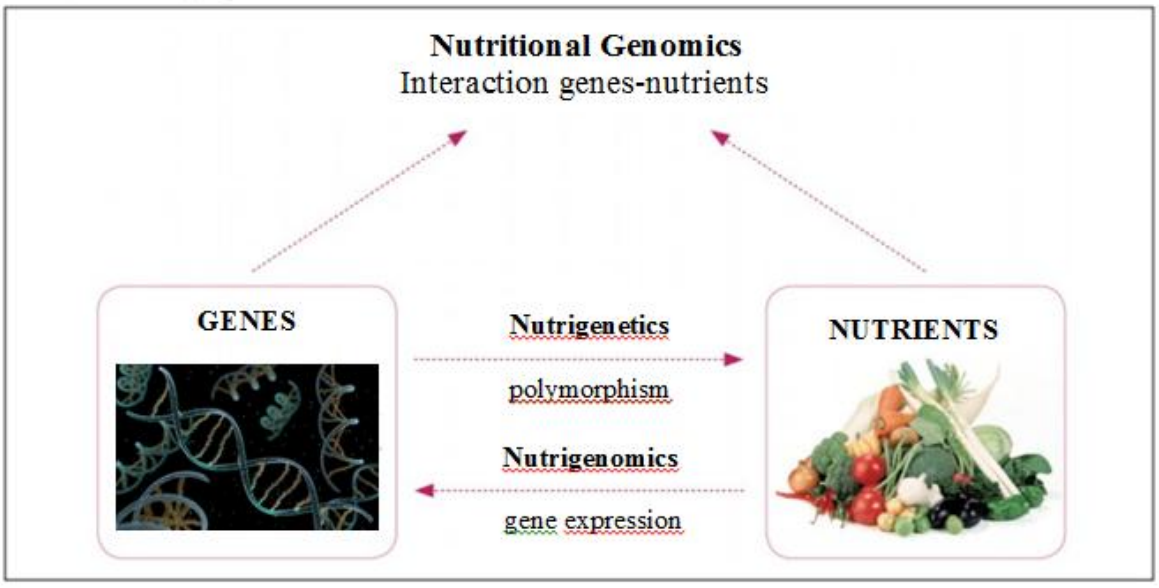

Figure 1: Descriptive scheme of the interactions gene-nutrient in nutritional genomics.