REVIEW

Metabolic syndrome: Evidences for a personalized nutrition

Pablo Perez-Martinez, Antonio Garcia-Rios*, Javier Delgado-Lista, Francisco Perez-Jimenez and Jose Lopez-Miranda*

Lipid and Atherosclerosis Unit, IMIBIC/Reina Sofia University Hospital/University of Cordoba, and CIBER Fisiopatologia Obesidad y Nutricion (CIBEROBN), Instituto de Salud Carlos III, Spain

Received: July 29, 2011
Revised: September 6, 2011
Accepted: September 23, 2011

Both insulin resistance and dyslipidaemia are determined by genetic and environmental factors. Depending on their expression and their function, gene variants may influence either insulin action or other metabolic traits. Nutrition also plays an important role in the development and progression of these conditions. Genetic background may interact with habitual dietary fat composition, affecting predisposition to insulin resistance syndrome and individual responsiveness to changes in dietary fat intake. In this context, nutrigenetics has emerged as a multidisciplinary field focusing on studying the interactions between nutritional and genetic factors and health outcomes. Due to the complex nature of gene–environment interactions, however, dietary therapy may require a ''personalized'' nutrition approach in the future. Although the results have not always been consistent, gene variants that affect primary insulin action, and particularly their interaction with the environment, are important modulators of glucose metabolism. The purpose of this review is to present some evidence of studies that have already demonstrated the significance of gene–nutrient interactions (adiponectin gene, Calpain-10, glucokinase regulatory protein, transcription factor 7-like 2, leptin receptor, scavenger receptor class B type I etc.) that influence insulin resistance in subjects with metabolic syndrome.

Keywords:
Diet / Gene–diet interaction / Metabolic syndrome / Nutrigenomics / Polymorphism

1 Introduction

Metabolic syndrome (MetS) represents a combination of cardiometabolic risk determinants, including central obesity, insulin resistance, hypertension, and dyslipidaemia [1]. This cluster of risk factors increases the risk of type 2 diabetes (T2D) and cardiovascular disease [2, 3]. The prevalence of MetS is growing, affecting almost a quarter of the global adult population, correlating with the global epidemic of obesity and T2D. Unfortunately, this rise has been observed not only in the Western world, but also in developing countries. The pathogenesis of MetS is complex and not completely understood, but the interaction of over-nutrition, lack of physical activity, and genetic factors are known to contribute to its development (Fig. 1) [4]. Although pharmacological interventions are available for minimizing or delaying the comorbidities associated with MetS, initial management for the vast majority of the affected population remains focused on lifestyle modification, consisting of sustainable changes in dietary habits and physical activity. Thus, lifestyle modification has generally been accepted as a cornerstone of treatment for MetS, with the expectation that an appropriate

Correspondence: Dr. Jose Lopez-Miranda, Reina Sofia University Hospital, Lipids and Atherosclerosis Research Unit, Avda. Menéndez Pidal, s/n. 14004 Córdoba, Spain
E-mail: jlopezmir@uco.es
Fax: +34-957050476

Abbreviations: ADIPOQ, adiponectin gene; **ADIPOR,** adiponectin receptor; **AIRg,** acute insulin response to glucose; **CAPN10,** calpain-10; **CHO,** carbohydrates; **CRP,** C-reactive protein; **GCKR,** glucokinase regulatory protein; **GOLDN,** Genetics of Lipid Lowering Drugs and Diet Network; **GWAS,** Genome-wide association studies; **HOMA-IR,** homeostasis model assessment of insulin resistance; **MedDiet,** Mediterranean diet; **MetS,** metabolic syndrome; **PDZK1,** PDZ domain containing 1; **SCARB1,** scavenger receptor class B type I; **SFAs,** saturated fatty acids; **SNPs,** single nucleotide polymorphisms; **TCF7L2,** transcription factor 7-like 2; **TG,** triglyceride; **T2D,** type 2 diabetes mellitus

*These authors contributed equally to this work.

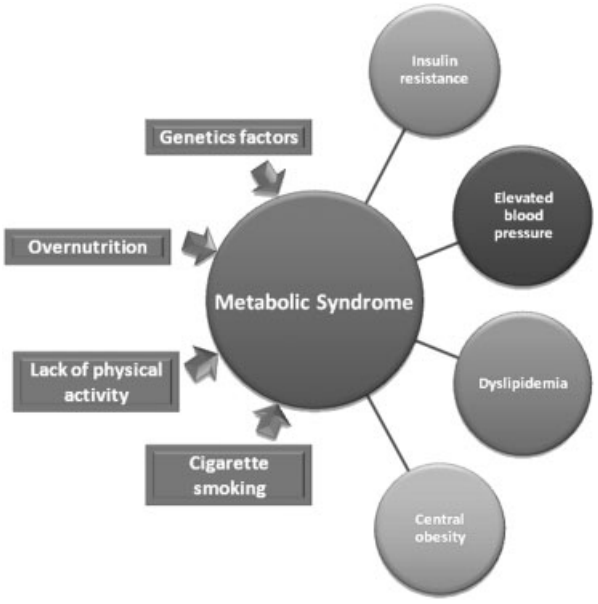

Figure 1. Common genetics variants and environmental factors may impact the development of the metabolic syndrome.

intake of energy and nutrients will improve its control and reduce the risk of complications.

The number of studies investigating gene–nutrient interactions related to MetS continues to grow, and has potential for reducing the risk of disease at the level of the individual genotype. Previous evidence suggests that some people are genetically predisposed to insulin resistance [5], a possible underlying mechanism for these metabolic disturbances. In this context, nutrigenetics has emerged as a multidisciplinary field focusing on studying the interactions between nutritional and genetic factors and health outcomes [6, 7]. Thus, it would be expected that general dietary recommendations may not be beneficial for all individuals. Due to the complex nature of gene–environment interactions, however, dietary therapy in combination with MetS may require a ''personalized'' nutrition approach. Although results have not always been consistent, gene variants that affect primary insulin action, and particularly their interaction with the environment, are important modulators of glucose metabolism and insulin resistance syndrome. Our aim is not to provide an exhaustive list of gene–diet interactions, but rather to show the current state of the art illustrating several evidences of studies that have already demonstrated the significance of gene–nutrient interactions that influence insulin resistance in subjects with MetS.

2 MetS and dietary therapy

Which is the most suitable dietary therapy in subjects with MetS? At this moment, this is quite a tricky question to answer because although we have some evidence regarding this matter, additional well-controlled intervention dietary studies are needed [8]. It is well known that dietary fat is an important environmental factor, with excessive exposure playing a key role in the development of MetS. In this context, epidemiological studies indicate that Western-style dietary patterns promote MetS, while diets enriched in fruits, vegetables, grains, fish, and low-fat dairy products play a protective role [9, 10]. In the PREDIMED study, the Mediterranean diet (MedDiet) with nuts significantly reduced MetS prevalence after 1 year, mostly because of increased reversion of prior MetS due to reduction in waist girth in spite of no weight loss, suggesting fat redistribution [11]. Interestingly, in a subgroup of this study, including the Reus PREDIMED Centre, some components of the MedDiet, such as olive oil, legumes, and red wine, were associated with lower prevalence of MetS [12]. Moreover, data including overweight, insulin-resistant patients also suggest that, compared with a low-fat diet, an MUFA-rich diet prevents the redistribution of body fat from peripheral to visceral adipose tissue without affecting total body weight [13]. Recently, Kastorini et al. conducted a meta-analysis of epidemiological studies and randomized controlled trials including 534 906 participants [14]. They observed that adherence to the MedDiet was associated with reduced risk of MetS. Additionally, results from clinical studies revealed the protective role of the MedDiet on components of MetS, such as waist circumference, high-density lipoprotein cholesterol, triglycerides (TGs), systolic and diastolic blood pressure, and glucose, whereas results from epidemiological studies also confirmed those of the clinical trials. Based on this evidence, the MedDiet appears to be a useful tool in the lifestyle management of MetS. This evidence has considerable implications for public health, because this dietary pattern can be easily adopted by all population groups and is a cost-effective means of primary and secondary prevention of MetS.

Over the last few years, more attention has been paid to the effect of the quality of dietary fat, independent of the total amount. As regards this concern, plasma fatty acid composition has been determined as a biomarker of habitual dietary fat intake and reflects the combination of dietary fat consumption and endogenous de novo fatty acid biosynthesis and metabolism. ω-3 polyunsaturated fatty acids (*n*-3 PUFA) are specially relevant, due to their potential ability to lower the risk of coronary heart disease and MetS [15–18]. However, limited and inconsistent data are available concerning the relation between *n*-3 PUFA and glucose metabolism. Furthermore, a recent prospective study including 36 328 women in the Women's Health Study suggests an increased risk of T2D, especially with higher intakes of *n*-3 PUFA [19]. This evidence supports the notion that general recommendations (MedDiet or *n*-3 PUFA) may not benefit equally all individuals, thus underlining the need to explain how certain dietary fatty acids may modulate the risk conferred by genetic susceptibility due to variation in the genes involved in the etiology of MetS.

3 The nutrigenomics revolution

After decades of experimental, epidemiological, and clinical research, it has become clear that the consumption of certain dietary patterns has a profound influence on health outcomes. However, despite our growing knowledge over the last years, the final proof linking the specific mechanisms and contributing role of the different dietary models and nutrients to its beneficial effects requires further investigations. Since completion of the human genome sequence, the landscape of nutrition research has undergone a rapid transformation. Genome-wide association studies (GWAS) by large international consortia are discovering genetic variants that contribute to metabolic diseases [20, 21]. Nevertheless, we lack nutrient information, which is essential for the development of dietary advice for the prevention and management of MetS and T2D. During the postgenomics era, the integrated application of approaches that are becoming available in functional genomics, such as proteomics, transcriptomics, metabonomics, lipidomics, epigenetics, microbiota, chronobiology, and others, are leading to a more highly integrated understanding of its positive effects on health [22–26]. Most of these techniques are being used in combination to improve our understanding of the influence of both specific nutrients and whole dietary patterns on the metabolic behaviour of our organism [27, 28]. Furthermore, there is a trend towards systemic approaches in which different technologies are combined and applied to the same sample, allowing physiological changes to be assessed more robustly throughout all the molecular layers of mRNA, protein, and metabolite changes. In this context, the recent advances in nutrigenetics and nutrigenomics, two fields with distinct approaches to elucidate the interaction between diet and genes but with a common ultimate goal to optimize health through the personalization of diet, are providing powerful approaches to unravel the complex relationship between nutritional molecules, genetic single nucleotide polymorphisms (SNPs), and the biological system as a whole [6, 7]. This scenario will increase our knowledge about new mechanisms of gene–nutrient interactions in MetS patients, which are needed for a ''personalized'' nutrition approach.

4 Preparatory search strategy

This review includes articles written in English language and published before June 30, 2011. Stage 1 of the review involved searching for publications using the most commonly used electronic database (Medline via PubMed). The MeSH terms used in the general search to identify gene–nutrient interactions that influence insulin resistance in MetS were selected from the following: gene–diet interaction AND MetS; gene–nutrient interaction AND MetS; Nutrigenetics AND MetS; Nutrigenomics AND MetS; polymorphism AND MetS; SNP AND MetS; LIPGENE AND nutrigenetics, or Genetics of Lipid Lowering Drugs and Diet Network (GOLDN) AND nutrigenetics. The authors decided how pertinent the item was, based on a reading of the title and abstract. Finally, we included only those studies that identify biomarkers related with glucose metabolism and/or insulin resistance state: insulin sensitivity index, homeostasis model assessment of insulin resistance (HOMA-IR), homeostasis model assessment of B-cell function (HOMA-B), fasting insulin, fasting glucose, glucose effectiveness, C peptide, first phase insulin secretion, and disposition index.

5 MetS and gene–nutrient interactions

It is widely known that the effect of dietary changes on plasma biomarker concentrations differs significantly between individuals. Moreover, there is increasing evidence that supports the concept that this variability in response is an intrinsic characteristic of the individual, rather than being the result of different dietary compliances with the experimental protocols. In this regard, in the last years two well-designed studies have been conducted to examine how gene–diet interactions influence susceptibility to MetS. The first of these was known as the GOLDN study, including 1200 subjects recruited from two genetically homogeneous and predominantly white racial areas (Minneapolis and Salt Lake City) [29]. The second, named the LIPGENE project, was a large European, multi-centre study including 486 subjects with MetS from eight countries (Ireland, UK, Norway, France, The Netherlands, Spain, Poland, and Sweden) [30]. Briefly, we present here some recent evidence in terms of gene–nutrient interactions, which modulate the degree of insulin resistance of MetS or some of its metabolic traits (Table 1).

5.1 Adiponectin

Adiponectin is an adipokine that is abundantly expressed in adipose tissue and sensitizes the body to insulin [31, 32]. Hypoadiponectinaemia, caused by interactions of genetic and environmental factors, appears to play an important causal role in insulin resistance, T2D, and MetS [33–35]. The adiponectin gene (ADIPOQ) is located on chromosome 3q27, which has been reported to be linked to T2D and MetS [36]. Based on the previous evidence, this is not surprising, considering that polymorphisms in the ADIPOQ and the adiponectin receptors, ADIPOR1 and ADIPOR2, may play a role in the pathogenesis of MetS [37]. Functional studies in animal models demonstrated that adiponectin attenuates insulin resistance by reducing TG content in muscle and liver [38]. In humans, associations have been found between several polymorphisms in ADIPOQ, ADIPOR1, and ADIPOR2 with adiponectin levels, insulin resistance, and MetS phenotypes [39, 40]. Therefore, factors such as a healthy diet, which leads to increases in adiponectin, might

Table 1. Studies showing evidences in terms of gene–nutrient interactions that modulate the degree of insulin resistance of the MetS or certain of its metabolic traits

Gene polymorphism	Population	Dietary factors	Biomarkers	Conclusion	Reference
rs266729 ADIPOQ, rs10753929 and rs10920533 ADIPOR1, rs6489323 ADIPOR2	452 MetS subjects LIPGENE cohort	SFA	Fasting insulin and HOMA-IR	A reduction in plasma SFA decreased insulin resistance in carriers of the minor allele of rs266729 ADIPOQ and rs10920533 ADIPOR1	Ferguson et al. [42]
rs2953171 CAPN10	452 MetS subjects LIPGENE cohort	SFA	Fasting insulin, HOMA-IR and glucose effectiveness	GG subjects with low plasma SFA levels showed lower fasting insulin and HOMA-IR, and higher glucose effectiveness compared to GA and AA	Perez-Martinez et al. [50]
rs1260326 GCKR	379 MetS subjects LIPGENE cohort	*n*-3 PUFA	Fasting insulin, C-peptide, HOMA-IR and CRP	CC subjects with the highest level of plasma *n*-3 PUFA showed lower fasting insulin, C-peptide, HOMA-IR, and CRP levels compared to CT and TT	Perez-Martinez et al. [54]
rs780094 GCKR	14 Cohorts comprising 48 000 participants of European descent	Whole grain	Fasting insulin	Greater whole-grain intake was associated with a smaller reduction in fasting insulin concentrations in those with the insulin-raising C allele	Nettleton et al. [55]
rs11196224 and rs290481 TCF7L2	450 MetS subjects LIPGENE cohort	SFA	Fasting insulin, HOMA-IR, AIRg	In homozygotes for the major allele of rs11196224, elevated plasma SFA was associated with increased fasting insulin and HOMA-IR. Major allele homozygotes for rs290481 showed a decrease AIRg, only when they were in the upper of the median group for SFA	Delgado-Lista et al. [61]
rs7903146 TCF7L2	MetS cases and matched controls from the LIPGENE-SU.VI.MAX ($n = 1754$)	SFA	Insulin sensitivity	High dietary SFA intake exacerbated MetS risk (odds ratio 2.35) and was associated with further impaired insulin sensitivity in the T allele carriers compared to the CC homozygotes	Phillips et al. [62]
rs3790433 LEPR	MetS cases and matched controls from the LIPGENE-SU.VI.MAX ($n = 1754$) and 463 subjects LIPGENE cohort	*n*-3 and *n*-6 PUFA	Hyperinsulinemia and insulin resistance	Low plasma *n*-3 and high n-6 PUFA status exacerbated the genetic risk conferred by GG homozygosity to hyperinsulinemia and insulin resistance	Phillips et al. [83]

Leptin receptor (LEPR).

be useful for improving such metabolic abnormalities. In this context, a previous intervention study demonstrated that C/C homozygous men for the −11377C>G SNP (rs266729) at ADIPOQ gene were significantly less insulin-resistant after consumption of the MUFA and carbohydrate (CHO)-rich diets compared with the saturated fatty acid (SFA)-rich diet [41]. These findings were not observed among female participants. In a cross-sectional analysis of 452 subjects with MetS participating in the LIPGENE dietary intervention cohort, two SNPs interacted with plasma SFAs to associate significantly with insulin and HOMA-IR (rs266729 in ADIPOQ, and rs10920533 in ADIPOR1) [42]. This study demonstrated that a reduction in plasma SFA decreased insulin resistance in carriers of the minor allele of rs266729 ADIPOQ and rs10920533 ADIPOR1. In agreement with these results, we can recommend a decrease in SFA consumption in the diet of MetS subjects carrying the minor allele of rs266729 ADIPOQ and/or rs10920533 ADIPOR1.

In a separate study, Warodomwichit et al. investigated the effect of ADIPOQ SNPs, −11377C>G (rs266729) and −11391G>A (rs17300539), on metabolic-related traits, and their modulation by dietary fat in white Americans from the GOLDN study [43]. Interestingly, the associations of the −11391G>A with BMI and obesity risk were modified by MUFA intake. In particular, in subjects with MUFA intake above the median (≥13% of energy intake), −11391A carriers had lower BMI (27.1 kg/m^2 for GA+AA versus 29.1 kg/m^2 for GG) and decreased obesity risk (odds ratio for −11391A = 0.52). In contrast they did not detect genotype-related differences for BMI or obesity in subjects with MUFA intake <13%. More recently, Alsaleh et al. [44] investigated the effect of the interaction between variants at the ADIPOQ gene locus, age, sex, BMI, ethnicity, and the switch of dietary SFA with MUFA or CHO on serum adiponectin concentrations. This randomized controlled trial (RISCK study) was conducted in white European subjects. Authors demonstrated that after the MUFA diet, −10066G>G (rs182052) subjects showed a 3.8% increase and GA+AA subjects a 2.6% decrease in serum adiponectin. In −10066 GG homozygotes, serum adiponectin increased with age after the MUFA diet and decreased after the low-fat diet. They concluded that in white −10066 GG homozygotes, an MUFA diet intake may help to increase adiponectin concentrations with advancing age.

5.2 Calpain-10

Calpain-10 (CAPN10) is an important molecule in the β-cell. It may be a fuel sensor and a determinant of insulin exocytosis, with actions at the mitochondria and plasma membrane, respectively. CAPN10 is located at 2q37 and encodes an ubiquitously expressed member of the calpain-like cysteine protease family. Genetic, as well as functional, data indicate that CAPN10 plays an important role in insulin resistance and intermediate phenotypes, including those associated with adipocytes [45]. Furthermore, the CAPN10 gene has been associated with several components of MetS, such as elevated plasma cholesterol levels [46], hypertriglyceridaemia [47], BMI [48], and hypertension [49]. In the LIPGENE cohort it was demonstrated that the rs2953171 CAPN10 genetic variant influences insulin sensitivity by interacting with plasma SFA levels in MetS subjects [50]. In particular, among subjects with low plasma SFA levels (below the median), the GG genotype was associated with lower fasting insulin concentration and HOMA-IR, and higher glucose effectiveness compared to subjects carrying the minor A allele (GA and AA). In contrast, higher fasting insulin and HOMA-IR, and lower glucose effectiveness were observed in the G/G subjects with the highest level of plasma SFA (above the median), compared to subjects with the A allele. There were no significant interactions between other groups of plasma fatty acids (MUFA or PUFA) and CAPN10 SNPs on glucose metabolism. Although functional studies were not performed, previous data indicate that some CAPN10 SNPs act as a regulator of CAPN10 expression (30).

As we mentioned above, the LIPGENE cohort is a carefully characterized population, and the mixed origin of the patients allows extrapolation of the results to the European population. In summary, these data suggest a beneficial effect of reducing the amount of SFA in the diet of MetS carriers of the GG rs2953171 genetic variant.

5.3 Glucokinase regulatory protein

In liver and pancreatic islet cells, glucokinase regulatory protein (GCKR) modifies glucokinase, which acts as a glucose sensor responsible for glucose phosphorylation in the first step of glycolysis. In an animal experimental model, adenoviral-mediated over-expression of GCKR in the liver increased glucokinase activity, which led to lowered blood glucose and increased TG concentrations [51]. In recent years, the minor T-allele of the rs780094 SNP (or rs1260326, a variant in high linkage disequilibrium), has been reported to be associated with decreased fasting glucose, increased serum TG and C-reactive protein (CRP) levels [52, 53]. This evidence supports the central position of GCKR in pathways regulating hepatic TG as well as glucose metabolism in humans. Another report derived from the LIPGENE study explored whether genetic variability at the GCKR gene locus was associated with the degree of insulin resistance, plasma concentrations of CRP, and *n*-3 PUFA. The authors observed that among subjects with *n*-3 PUFA levels below the population median, the CC genotype was associated with higher fasting insulin concentrations, C-peptide levels, and HOMA-IR compared to subjects carrying the minor T-allele. In contrast, CC subjects with the highest level of plasma *n*-3 PUFA showed lower fasting insulin concentrations, C-peptide levels, and HOMA-IR, compared to subjects

with the T-allele. Moreover, they also showed lower CRP levels [54]. These novel findings support the hypothesis that the GCKR rs1260326-P446L polymorphism influences insulin resistance by interacting with plasma *n*-3 PUFA levels in MetS subjects. Based on these findings, and on the observed genotype-dependent responses, we can infer that a recommendation to increase *n*-3 PUFA could have an even more beneficial effect on insulin resistance and inflammatory markers only among MetS patients carrying the C/C genotype, which might in turn have implications with respect to cardiovascular risk. On the other hand, Nettleton et al. observed that the rs780094 SNP interacted with whole-grain intake for fasting insulin, where greater whole-grain intake was associated with a smaller reduction in fasting insulin concentrations in those with the insulin-raising allele [55]. Because this locus has also been associated with postprandial TG metabolism [52, 56] as well as markers of insulin resistance and inflammation, it can clearly be considered a significant gene–diet interaction that modulates the risk for MetS.

5.4 Transcription factor 7-like 2

Transcription factor 7-like 2 (TCF7L2) are transcription factors of Wnt, a family of ligands with multiple functions, from adipocyte differentiation to pancreatic β-cell function, and cortisol/aldosterone secretion [57]. Since 2006, GWAS studies have identified TCF7L2 gene variations as the most predictive identifiable factors promoting T2D development [58, 59]. These SNPs do not seem to predict the MetS, but they are not well characterized among subjects with MetS [60]. In the LIPGENE study, Delgado-Lista et al. investigated the associations between gene variants of TCF7L2 and clinical features of the MetS, and their interaction with non-genetic factors, including plasma SFA concentration and insulin resistance [61]. It was observed that variations at the TCF7L2 gene locus were significantly associated with several clinical features including plasma lipid concentrations, CHO metabolism, blood pressure, and markers of inflammation/coagulation. Some of these variables seemed to be independent of plasma SFA levels or insulin resistance, whereas others were clearly associated with these factors. SFA modulated rs11196224 effects on markers of inflammation/coagulation (IL-6 and tPA levels) and insulin resistance, rs17685538 on blood pressure, and rs290481 effects on markers of insulin secretion. In the context of glucose metabolism, elevated plasma concentration of SFA was associated with increased insulin and HOMA-IR in homozygotes for the major allele of rs11196224, suggesting enhanced insulin resistance. Moreover, the major allele homozygotes for rs290481 showed a decrease in the acute insulin response to glucose (AIRg = first phase insulin response) compared to the minor allele carriers, only when they were in the upper part of the median group for SFA. In the same line Phillips et al. in the LIPGENE-SU.VI.MAX study of MetS cases and matched controls, including 1754 subjects, determined potential interactions with dietary fat intake [62]. They demonstrated that high dietary SFA intake ($\geq$15.5% energy) exacerbated MetS risk (odds ratio 2.35) and was associated with further impaired insulin sensitivity in the T-allele carriers of rs7903146 compared to the CC homozygotes and particularly to the T-allele carriers with the lowest SFA intake. In contrast, no significant genotype effect on MetS risk or insulin sensitivity was evident among low-SFA consumers. Interestingly, three main conclusions may be extracted from these studies: first, the extraordinary pleiotropical phenotype associations observed with TCF7L2 gene variants; second, the modulation of these interactions by life-style factors like dietary SFA and insulin sensitivity; third, that variations at the TCF7L2 gene influences MetS risk, which is modulated by dietary SFA intake. In conclusion, data from these previous studies suggest a beneficial effect of decreasing the amount of SFA in the diet of homozygotes for the major allele of rs11196224 and rs290481 and in those carriers of the minor T allele of rs7903146.

5.5 Scavenger receptor class B type I and PDZ domain containing 1

The scavenger receptor class B type I (SCARB1) is part of a family of receptors that bind modified lipoproteins and was identified as an HDL receptor involved in selective uptake of cholesterol esters [63]. The SCARB1 gene is located in 12q24, and several polymorphisms in this region have been associated, in relation to dietary fat, with fasting and postprandial lipid traits [64–66]. Moreover, previous data suggest that the presence of the A allele at the SCARB1 exon 1 polymorphism was associated with a significant increase in insulin sensitivity after the consumption of an MUFA-rich diet when compared with the effects observed in GG healthy subjects [67]. On the other hand, the expression of SCARB1 protein is controlled by its adaptor PDZ domain containing 1 (PDZK1) in the liver [68], a protein composed of four modular PDZ-interacting domains that bind at the C terminus of SCARB1 [69]. PDZK1 gene has been located at 1q21, a chromosomal region that has been linked repeatedly with multiple metabolic abnormalities, such as hypertension, abdominal obesity, and MetS [70, 71]. Recently, Junyent et al. investigated the potential association of genetic variants (i33968C>T, i15371G>A, and i19738C>T) at the PDZK1 gene with lipoprotein levels and the MetS-related phenotypes and whether those SNPs interact with dietary factors to modulate MetS risk [72]. In the GOLDN study, the PDZK1 i33968C>T SNP was associated with MetS, mainly driven by the association of the minor T allele with higher plasma TG and VLDL, and lower adiponectin concentrations than in CC homozygous. In a next step, they found a significant gene × BMI × diet interaction, in which the deleterious association of the i33968T allele with MetS was observed in obese subjects with

high PUFA and CHO intakes. Interestingly, a protective effect in non-obese subjects with high PUFA intake was observed. This interaction offers the potential to identify lifestyle changes via dietary fat. Specifically, among non-obese carriers of the i33968T allele, dietary intake of PUFA should be increased, whereas the opposite should be recommended in obese subjects.

5.6 Other gene loci

In the last decade, we and others published some extensive reviews including the evidence linking a number of gene–diet interactions (i.e. APOE, FABP2, APOCIII, HL (hepatic lipase), PPAR-γ, IL-1β, perilipin etc.) to the modulation of MetS [4, 73–77]. Moreover, in the last 3 years, researchers identified an explosion of novel interactions involved in MetS susceptibility (ApoA-1 [78], ApoB [78], ApoA5 [79], lymphotoxin-α [80], TNF-α [80], IL-6 [80], CLOCK [81], complement component 3 [82], leptin receptor [83], cyclin-dependent kinase 5 regulatory subunit-associated protein 1-like 1 [84], PPAR-δ [85], NOS3 [86], Acetyl-CoA carboxylase β [87], acyl CoA synthetase 1 [88], signal transducer and activator of transcription 3 [89] etc). This increasing knowledge about the relationship between genetic and environmental components may facilitate the choice of more effective and specific measures for MetS prevention based on ''personalized'' nutrition.

5.7 Future directions and conclusions

The shift towards ''personalized'' nutritional advice is an attractive proposition. However, for the future, it is essential to take into account the following considerations:

(i) Consistency is still low and replication is a major need for gene–diet interactions studies because the complexity and variability of the designs may add even more bias than for other experimental approaches.
(ii) More studies with a better epidemiological design and diet interventions and measures are needed to estimate the relative contributions of diet and genetic predisposition to MetS.
(iii) GWAS studies need to include diet and other environmental exposures, such as smoking, physical activity, or ethnic group, in the interaction between genetic variation and disease association.
(iv) Research must look into the potential mechanisms involved in the dramatic individual variability response observed in the gene–diet interactions reported by nutrigenetic studies.
(v) Emerging evidence suggests the important role of microRNAs in the development and progression of several diseases. This issue, together with epigenetics, must be investigated in relation with nutrition and MetS abnormalities.

In conclusion although we cannot perform interventions to change genetic constitution, environmental interventions may reduce insulin resistance and other related-metabolic traits, and individuals might attenuate the harmful effects by dietary changes. In this review, we have presented evidence of studies that have already demonstrated the significance of gene–nutrient interactions that influence insulin resistance in subjects with MetS. Advances in the field of nutrigenetics are expected to open new paths in genome-customized diets for MetS prevention.

This work was supported in part by public funds: research grants from the Spanish Ministry of Science and Innovation (AGL 2004-07907, AGL2006-01979, and AGL2009-12270 to J. L.-M., SAF07-62005 to F. P.-J., and FIS PI10/01041 to P. P.-M., PI10/02412 to F. P.-J.); Consejería de Economía, Innovación y Ciencia, Proyectos de Investigación de Excelencia, Junta de Andalucía (P06-CTS-01425 to J. L.-M., CTS5015 and AGR922 to F. P.-J.); Consejería de Salud, Junta de Andalucía (06/128, 07/43, and PI0193/09 to J. L.-M., 06/129 to F. P.-J., 0118/08 to F. F.-J., PI-0252/09 to J. D.-L., and PI-0058/10 to P. P.-M.); Fondo Europeo de Desarrollo Regional (FEDER); Centro de Excelencia Investigadora en Aceite de Oliva y Salud (CEAS). The CIBEROBN is an initiative of the Instituto de Salud Carlos III, Madrid, Spain. A. G.-R. is supported by a research contract of ISCIII (Programa Río-Hortega).

The authors have declared no conflict of interest.

6 References

[1] Reaven, G., Metabolic syndrome: Pathophysiology and implications for management of cardiovascular disease. *Circulation* 2002, *106*, 286–288.

[2] Grundy, S. M., Metabolic syndrome: connecting and reconciling cardiovascular and diabetes worlds. *J. Am. Coll. Cardiol.* 2006, *47*, 1093–1100.

[3] Cornier, M. A., Dabelea, D., Hernandez, T. L., Lindstrom, R. C. et al., The metabolic syndrome. *Endocr. Rev.* 2008, *29*, 777–822.

[4] Roche, H. M., Phillips, C., Gibney, M. J., The metabolic syndrome: the crossroads of diet and genetics. *Proc. Nutr. Soc.* 2005, *64*, 371–377.

[5] Lopez-Miranda, J., Perez-Martinez, P., Marin, C., Fuentes, F. et al., Dietary fat, genes and insulin sensitivity. *J. Mol. Med.* 2007, *85*, 213–226.

[6] Ordovas, J. M., Mooser, V., Nutrigenomics and nutrigenetics. *Curr. Opin. Lipidol.* 2004, *15*, 101–108.

[7] Perez-Martinez, P., Lopez-Miranda, J., Ordovas, J. M., Perez-Jimenez, F., Nutrition in the age of genomics: towards a personalized diet. *Med. Clin. (Barc.)* 2008, *130*, 103–108.

[8] Perez-Martinez, P., Garcia-Rios, A., Delgado-Lista, J., Perez-Jimenez, F., Lopez-Miranda, J., Mediterranean diet rich in olive oil and obesity, metabolic syndrome and diabetes mellitus. *Curr. Pharm. Des.* 2011, *17*, 769–777.

[9] Pereira, M. A., Kartashov, A. I., Ebbeling, C. B., Van Horn, L. et al., Fast-food habits, weight gain, and insulin resistance

(the CARDIA study): 15-year prospective analysis. *Lancet* 2005, *365*, 36–42.

[10] Lutsey, P. L., Steffen, L. M., Stevens, J., Dietary intake and the development of the metabolic syndrome: the Atherosclerosis Risk in Communities study. *Circulation* 2008, *117*, 754–761.

[11] Salas-Salvado, J., Fernandez-Ballart, J., Ros, E., Martinez-Gonzalez, M. A. et al., Effect of a Mediterranean diet supplemented with nuts on metabolic syndrome status: one-year results of the PREDIMED randomized trial. *Arch. Intern. Med.* 2008, *168*, 2449–2458.

[12] Babio, N., Bullo, M., Basora, J., Martinez-Gonzalez, M. A. et al., Adherence to the Mediterranean diet and risk of metabolic syndrome and its components. *Nutr. Metab. Cardiovasc. Dis.* 2009, *19*, 563–570.

[13] Paniagua, J. A., Gallego de la Sacristana, A., Romero, I., Vidal-Puig, A. et al., Monounsaturated fat-rich diet prevents central body fat distribution and decreases postprandial adiponectin expression induced by a carbohydrate-rich diet in insulin-resistant subjects. *Diabetes Care* 2007, *30*, 1717–1723.

[14] Kastorini, C. M., Milionis, H. J., Esposito, K., Giugliano, D. et al., The effect of Mediterranean diet on metabolic syndrome and its components: a meta-analysis of 50 studies and 534,906 individuals. *J. Am. Coll. Cardiol.* 2011, *57*, 1299–1313.

[15] Jenkins, D. J., Josse, A. R., Dorian, P., Burr, M. L. et al., Heterogeneity in randomized controlled trials of long chain (fish) omega-3 fatty acids in restenosis, secondary prevention and ventricular arrhythmias. *J. Am. Coll. Nutr.* 2008, *27*, 367–378.

[16] Noel, S. E., Newby, P. K., Ordovas, J. M., Tucker, K. L., Adherence to an (*n*−3) fatty acid/fish intake pattern is inversely associated with metabolic syndrome among Puerto Rican adults in the Greater Boston area. *J. Nutr.* 2010, *140*, 1846–1854.

[17] Albert, C. M., Campos, H., Stampfer, M. J., Ridker, P. M. et al., Blood levels of long-chain *n*−3 fatty acids and the risk of sudden death. *N. Engl. J. Med.* 2002, *346*, 1113–1118.

[18] Paniagua, J. A., Perez-Martinez, P., Tierney, A.C., Gjelstad, I. M. F. et al., A low-fat high-carbohydrate diet supplemented with long-chain *n*−3 PUFA reduces the risk of the metabolic syndrome. *Atherosclerosis* 2011, *218*, 443–450.

[19] Djousse, L., Gaziano, J. M., Buring, J. E., Lee, I. M., Dietary omega-3 fatty acids and fish consumption and risk of type 2 diabetes. *Am. J. Clin. Nutr.* 2011, *93*, 143–150.

[20] Hirschhorn, J. N., Gajdos, Z. K., Genome-wide association studies: results from the first few years and potential implications for clinical medicine. *Annu. Rev. Med.* 2011, *62*, 11–24.

[21] Billings, L. K., Florez, J. C., The genetics of type 2 diabetes: what have we learned from GWAS? *Ann. N. Y. Acad. Sci.* 2010, *1212*, 59–77.

[22] Kontush, A., Chapman, M. J., Lipidomics as a tool for the study of lipoprotein metabolism. *Curr. Atheroscler. Rep.* 2010, *12*, 194–201.

[23] Oresic, M., Metabolomics, a novel tool for studies of nutrition, metabolism and lipid dysfunction. *Nutr. Metab. Cardiovasc. Dis.* 2009, *19*, 816–824.

[24] Garaulet, M., Madrid, J. A., Chronobiology, genetics and metabolic syndrome. *Curr. Opin. Lipidol.* 2009, *20*, 127–134.

[25] Tilg, H., Obesity, metabolic syndrome, and microbiota: multiple interactions. *J. Clin. Gastroenterol.* 2010, *44*, S16–S18.

[26] Gallou-Kabani, C., Junien, C., Nutritional epigenomics of metabolic syndrome: new perspective against the epidemic. *Diabetes* 2005, *54*, 1899–1906.

[27] Roberts, M. A., Mutch, D. M., German, J. B., Genomics: food and nutrition. *Curr. Opin. Biotechnol.* 2001, *12*, 516–522.

[28] Kaput, J., Ordovas, J. M., Ferguson, L., van Ommen, B. et al., The case for strategic international alliances to harness nutritional genomics for public and personal health. *Br. J. Nutr.* 2005, *94*, 623–632.

[29] GOLDN. Genetics of lipid lowering drugs and diet network. [Accessed March 12, 2008].

[30] Shaw, D. I., Tierney, A. C., McCarthy, S., Upritchard, J. et al., LIPGENE food-exchange model for alteration of dietary fat quantity and quality in free-living participants from eight European countries. *Br. J. Nutr.* 2009, *101*, 750–759.

[31] Berg, A. H., Combs, T. P., Du, X., Brownlee, M., Scherer, P. E., The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. *Nat. Med.* 2001, *7*, 947–953.

[32] Yamauchi, T., Kamon, J., Minokoshi, Y., Ito, Y. et al., Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat. Med.* 2002, *8*, 1288–1295.

[33] Tschritter, O., Fritsche, A., Thamer, C., Haap, M. et al., Plasma adiponectin concentrations predict insulin sensitivity of both glucose and lipid metabolism. *Diabetes* 2003, *52*, 239–243.

[34] Ryo, M., Nakamura, T., Kihara, S., Kumada, M. et al., Adiponectin as a biomarker of the metabolic syndrome. *Circ. J.* 2004, *68*, 975–981.

[35] Weyer, C., Funahashi, T., Tanaka, S., Hotta, K. et al., Hypoadiponectinemia in obesity and type 2 diabetes: Close association with insulin resistance and hyperinsulinemia. *J. Clin. Endocrinol. Metab.* 2001, *86*, 1930–1935.

[36] Vasseur, F., Helbecque, N., Dina, C., Lobbens, S. et al., Single-nucleotide polymorphism haplotypes in the both proximal promoter and exon 3 of the APM1 gene modulate adipocyte-secreted adiponectin hormone levels and contribute to the genetic risk for type 2 diabetes in French Caucasians. *Hum. Mol. Genet.* 2002, *11*, 2607–2614.

[37] Vasseur, F., Meyre, D., Froguel, P., Adiponectin, type 2 diabetes and the metabolic syndrome: lessons from human genetic studies. *Exp. Rev. Mol. Med.* 2006, *8*, 1–12.

[38] Yamauchi, T., Kamon, J., Waki, H., Terauchi, Y. et al., The fat-derived hormone adiponectin reverses insulin resistance associated with both lipoatrophy and obesity. *Nat. Med.* 2001, *7*, 941–946.

[39] Menzaghi, C., Trischitta, V., Doria, A., Genetic influences of adiponectin on insulin resistance, type 2 diabetes, and cardiovascular disease. *Diabetes* 2007, *56*, 1198–1209.

[40] Sheng, T., Yang, K., Adiponectin and its association with insulin resistance and type 2 diabetes. *J. Genet. Genomics* 2008, *35*, 321–326.

[41] Perez-Martinez, P., Lopez-Miranda, J., Cruz-Teno, C., Delgado-Lista, J. et al., Adiponectin gene variants are associated with insulin sensitivity in response to dietary fat consumption in Caucasian men. *J. Nutr.* 2008, *138*, 1609–1614.

[42] Ferguson, J. F., Phillips, C. M., Tierney, A. C., Perez-Martinez, P. et al., Gene-nutrient interactions in the metabolic syndrome: single nucleotide polymorphisms in ADIPOQ and ADIPOR1 interact with plasma saturated fatty acids to modulate insulin resistance. *Am. J. Clin. Nutr.* 2010, *91*, 794–801.

[43] Warodomwichit, D., Shen, J., Arnett, D. K., Tsai, M. Y. et al., ADIPOQ polymorphisms, monounsaturated fatty acids, and obesity risk: the GOLDN study. *Obesity (Silver Spring)* 2009, *17*, 510–517.

[44] Alsaleh, A., O'Dell, S. D., Frost, G. S., Griffin, B. A. et al., Single nucleotide polymorphisms at the ADIPOQ gene locus interact with age and dietary intake of fat to determine serum adiponectin in subjects at risk of the metabolic syndrome. *Am. J. Clin. Nutr.* 2011, *94*, 262–269.

[45] Saez, M. E., Gonzalez-Sanchez, J. L., Ramirez-Lorca, R., Martinez-Larrad, M. T. et al., The CAPN10 gene is associated with insulin resistance phenotypes in the Spanish population. *PLoS One* 2008, *3*, e2953.

[46] Wu, B., Takahashi, J., Fu, M., Cheng, H. et al., Variants of calpain-10 gene and its association with type 2 diabetes mellitus in a Chinese population. *Diabetes Res. Clin. Pract.* 2005, *68*, 155–161.

[47] Carlsson, E., Fredriksson, J., Groop, L., Ridderstrale, M., Variation in the calpain-10 gene is associated with elevated triglyceride levels and reduced adipose tissue messenger ribonucleic acid expression in obese Swedish subjects. *J. Clin. Endocrinol. Metab.* 2004, *89*, 3601–3605.

[48] Shima, Y., Nakanishi, K., Odawara, M., Kobayashi, T., Ohta, H., Association of the SNP-19 genotype 22 in the calpain-10 gene with elevated body mass index and hemoglobin A1c levels in Japanese. *Clin. Chim. Acta* 2003, *336*, 89–96.

[49] Garant, M. J., Kao, W. H., Brancati, F., Coresh, J. et al., SNP43 of CAPN10 and the risk of type 2 diabetes in African-Americans: the Atherosclerosis Risk in Communities Study. *Diabetes* 2002, *51*, 231–237.

[50] Perez-Martinez, P., Delgado-Lista, J., Garcia-Rios, A., Ferguson, J. F. et al., Calpain-10 interacts with plasma saturated fatty acid concentrations to influence insulin resistance in individuals with the metabolic syndrome. *Am. J. Clin. Nutr.* 2011, *93*, 1136–1141.

[51] O'Doherty, R. M., Lehman, D. L., Telemaque-Potts, S., Newgard, C. B., Metabolic impact of glucokinase overexpression in liver: Lowering of blood glucose in fed rats is accompanied by hyperlipidemia. *Diabetes* 1999, *48*, 2022–2027.

[52] Perez-Martinez, P., Corella, D., Shen, J., Arnett, D. K. et al., Association between glucokinase regulatory protein (GCKR) and apolipoprotein A5 (APOA5) gene polymorphisms and triacylglycerol concentrations in fasting, postprandial, and fenofibrate-treated states. *Am. J. Clin. Nutr.* 2009, *89*, 391–399.

[53] Orho-Melander, M., Melander, O., Guiducci, C., Perez-Martinez, P. et al., Common missense variant in the glucokinase regulatory protein gene is associated with increased plasma triglyceride and C-reactive protein but lower fasting glucose concentrations. *Diabetes* 2008, *57*, 3112–3121.

[54] Perez-Martinez, P., Delgado-Lista, J., Garcia-Rios, A., Mc Monagle, J. et al., Glucokinase regulatory protein genetic variant interacts with omega-3 PUFA to influence insulin resistance and inflammation in metabolic syndrome. *PLoS One* 2011, *6*, e20555.

[55] Nettleton, J. A., McKeown, N. M., Kanoni, S., Lemaitre, R. N. et al., Interactions of dietary whole-grain intake with fasting glucose- and insulin-related genetic loci in individuals of European descent: A meta-analysis of 14 cohort studies. *Diabetes Care* 2010, *33*, 2684–2691.

[56] Shen, H., Pollin, T. I., Damcott, C. M., McLenithan, J. C. et al., Glucokinase regulatory protein gene polymorphism affects postprandial lipemic response in a dietary intervention study. *Hum. Genet.* 2009, *126*, 567–574.

[57] Ross, S. E., Hemati, N., Longo, K. A., Bennett, C. N. et al., Inhibition of adipogenesis by Wnt signaling. *Science* 2000, *289*, 950–953.

[58] Florez, J. C., Jablonski, K. A., Bayley, N., Pollin, T. I. et al., TCF7L2 polymorphisms and progression to diabetes in the Diabetes Prevention Program. *N. Engl. J. Med.* 2006, *355*, 241–250.

[59] Florez, J. C., Newly identified loci highlight beta cell dysfunction as a key cause of type 2 diabetes: Where are the insulin resistance genes? *Diabetologia* 2008, *51*, 1100–1110.

[60] Marzi, C., Huth, C., Kolz, M., Grallert, H. et al., Variants of the transcription factor 7-like 2 gene (TCF7L2) are strongly associated with type 2 diabetes but not with the metabolic syndrome in the MONICA/KORA surveys. *Horm. Metab. Res.* 2007, *39*, 46–52.

[61] Delgado-Lista, J., Perez-Martinez, P., Garcia-Rios, A., Phillips, C. M. et al., Pleiotropic effects of TCF7L2 gene variants and its modulation in the metabolic syndrome: from the LIPGENE study. *Atherosclerosis* 2011, *214*, 110–116.

[62] Phillips, C. M., Goumidi, L., Bertrais, S., Field, M. R. et al., Dietary saturated fat, gender and genetic variation at the TCF7L2 locus predict the development of metabolic syndrome. *J. Nutr. Biochem.* 2011, Epub ahead of print, DOI: 10.1016/j.jnutbio.2010.11.020.

[63] Acton, S., Rigotti, A., Landschulz, K. T., Xu, S. et al., Identification of scavenger receptor SR-BI as a high density lipoprotein receptor. *Science* 1996, *271*, 518–520.

[64] Perez-Martinez, P., Lopez-Miranda, J., Ordovas, J. M., Bellido, C. et al., Postprandial lipemia is modified by the presence of the polymorphism present in the exon 1 variant at the SR-BI gene locus. *J. Mol. Endocrinol.* 2004, *32*, 237–245.

[65] Tanaka, T., Delgado-Lista, J., Lopez-Miranda, J., Perez-Jimenez, F. et al., Scavenger receptor class B type I

(SCARB1) c.1119C>T polymorphism affects postprandial triglyceride metabolism in men. *J. Nutr.* 2007, *137*, 578–582.

[66] Perez-Martinez, P., Ordovas, J. M., Lopez-Miranda, J., Gomez, P. et al., Polymorphism exon 1 variant at the locus of the scavenger receptor class B type I gene: Influence on plasma LDL cholesterol in healthy subjects during the consumption of diets with different fat contents. *Am. J. Clin. Nutr.* 2003, *77*, 809–813.

[67] Perez-Martinez, P., Perez-Jimenez, F., Bellido, C., Ordovas, J. M. et al., A polymorphism exon 1 variant at the locus of the scavenger receptor class B type I (SCARB1) gene is associated with differences in insulin sensitivity in healthy people during the consumption of an olive oil-rich diet. *J. Clin. Endocrinol. Metab.* 2005, *90*, 2297–2300.

[68] Fenske, S. A., Yesilaltay, A., Pal, R., Daniels, K. et al., Overexpression of the PDZ1 domain of PDZK1 blocks the activity of hepatic scavenger receptor, class B, type I by altering its abundance and cellular localization. *J. Biol. Chem.* 2008, *283*, 22097–22104.

[69] Yesilaltay, A., Kocher, O., Rigotti, A., Krieger, M., Regulation of SR-BI-mediated high-density lipoprotein metabolism by the tissue-specific adaptor protein PDZK1. *Curr. Opin. Lipidol.* 2005, *16*, 147–152.

[70] Harrap, S. B., Wong, Z. Y., Scurrah, K. J., Lamantia, A., Genome-wide linkage analysis of population variation in high-density lipoprotein cholesterol. *Hum. Genet.* 2006, *119*, 541–546.

[71] Ng, M. C., So, W. Y., Lam, V. K., Cockram, C. S. et al., Genome-wide scan for metabolic syndrome and related quantitative traits in Hong Kong Chinese and confirmation of a susceptibility locus on chromosome 1q21-q25. *Diabetes* 2004, *53*, 2676–2683.

[72] Junyent, M., Arnett, D. K., Tsai, M. Y., Kabagambe, E. K. et al., Genetic variants at the PDZ-interacting domain of the scavenger receptor class B type I interact with diet to influence the risk of metabolic syndrome in obese men and women. *J. Nutr.* 2009, *139*, 842–848.

[73] Ordovas, J. M., Shen, J., Gene-environment interactions and susceptibility to metabolic syndrome and other chronic diseases. *J. Periodontol.* 2008, *79*, 1508–1513.

[74] Andreassi, M. G., Metabolic syndrome, diabetes and atherosclerosis: influence of gene-environment interaction. *Mutat. Res.* 2009, *667*, 35–43.

[75] Lopez-Miranda, J., Perez-Martinez, P., Marin, C., Fuentes, F. et al., Dietary fat, genes and insulin sensitivity. *J. Mol. Med. (Berl.)* 2007, *85*, 213–226.

[76] Phillips, C., Lopez-Miranda, J., Perez-Jimenez, F., McManus, R., Roche, H. M., Genetic and nutrient determinants of the metabolic syndrome. *Curr. Opin. Cardiol.* 2006, *21*, 185–193.

[77] Phillips, C. M., Tierney, A. C., Roche, H. M., Gene-nutrient interactions in the metabolic syndrome. *J. Nutrigenet. Nutrigenomics* 2008, *1*, 136–151.

[78] Phillips, C. M., Goumidi, L., Bertrais, S., Field, M. R. et al., Gene-nutrient interactions and gender may modulate the association between ApoA1 and ApoB gene polymorphisms and metabolic syndrome risk. *Atherosclerosis* 2011, *214*, 408–414.

[79] Mattei, J., Demissie, S., Tucker, K. L., Ordovas, J. M., Apolipoprotein A5 polymorphisms interact with total dietary fat intake in association with markers of metabolic syndrome in Puerto Rican older adults. *J. Nutr.* 2009, *139*, 2301–2308.

[80] Phillips, C. M., Goumidi, L., Bertrais, S., Ferguson, J. F. et al., Additive effect of polymorphisms in the IL-6, LTA, and TNF-alpha genes and plasma fatty acid level modulate risk for the metabolic syndrome and its components. *J. Clin. Endocrinol. Metab.* 2010, *95*, 1386–1394.

[81] Garaulet, M., Lee, Y. C., Shen, J., Parnell, L. D. et al., CLOCK genetic variation and metabolic syndrome risk: modulation by monounsaturated fatty acids. *Am. J. Clin. Nutr.* 2009, *90*, 1466–1475.

[82] Phillips, C. M., Goumidi, L., Bertrais, S., Ferguson, J. F. et al., Complement component 3 polymorphisms interact with polyunsaturated fatty acids to modulate risk of metabolic syndrome. *Am. J. Clin. Nutr.* 2009, *90*, 1665–1673.

[83] Phillips, C. M., Goumidi, L., Bertrais, S., Field, M. R. et al., Leptin receptor polymorphisms interact with polyunsaturated fatty acids to augment risk of insulin resistance and metabolic syndrome in adults. *J. Nutr.* 2010, *140*, 238–244.

[84] Miyaki, K., Oo, T., Song, Y., Lwin, H. et al., Association of a cyclin-dependent kinase 5 regulatory subunit-associated protein 1-like 1 (CDKAL1) polymorphism with elevated hemoglobin A(c) levels and the prevalence of metabolic syndrome in Japanese men: interaction with dietary energy intake. *Am. J. Epidemiol.* 2010, *172*, 985–991.

[85] Robitaille, J., Gaudet, D., Perusse, L., Vohl, M. C., Features of the metabolic syndrome are modulated by an interaction between the peroxisome proliferator-activated receptor-delta -87T>C polymorphism and dietary fat in French-Canadians. *Int. J. Obes. (Lond.)* 2007, *31*, 411–417.

[86] Ferguson, J. F., Phillips, C. M., McMonagle, J., Perez-Martinez, P. et al., NOS3 gene polymorphisms are associated with risk markers of cardiovascular disease, and interact with omega-3 polyunsaturated fatty acids. *Atherosclerosis* 2010, *211*, 539–544.

[87] Phillips, C. M., Goumidi, L., Bertrais, S., Field, M. R. et al., ACC2 gene polymorphisms, metabolic syndrome, and gene-nutrient interactions with dietary fat. *J. Lipid Res.* 2010, *51*, 3500–3507.

[88] Phillips, C. M., Goumidi, L., Bertrais, S., Field, M. R. et al., Gene-nutrient interactions with dietary fat modulate the association between genetic variation of the ACSL1 gene and metabolic syndrome. *J. Lipid Res.* 2010, *51*, 1793–1800.

[89] Phillips, C. M., Goumidi, L., Bertrais, S., Field, M. R. et al., Dietary saturated fat modulates the association between STAT3 polymorphisms and abdominal obesity in adults. *J. Nutr.* 2009, *139*, 2011–2017.

