Chapter 10

Genomic Determinants of Mediterranean Diet Success

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INTRODUCTION

The Mediterranean diet is recognized as one of the most healthy in the world, and variations of it seem to be the most successful nutritional regimens for reducing cardiovascular risk factors [1–5]. Why is the Mediterranean diet apparently so beneficial? In a recent review, Ordovas et al. [6] speculated that:

> *the Mediterranean diet may be closer to the ancestral foods that were part of human development and our metabolism may have evolved to work optimally on such a diet rather than with the current diets richer in saturated fat and highly refined and processed foods. Therefore, it is possible that alleles that are associated with increased disease risk may be silenced in the presence of that more ancestral and traditional diet and lifestyle. This knowledge may provide the basis for successful public health as well individual approaches for disease prevention.*

Alleles refers to the presence of common genetic variants that can modify the way an individual responds to diets of differing composition. Two things are known for certain: genes affect response to diet, and diet affects gene expression (for example, personal genetic variation affects response to ultraviolet light, and ultraviolet light in turn affects gene expression). In general, the way genetic variation affects response to nutrients in the diet is termed *nutrigenetics*, whereas *nutrigenomics* is the term used for the effect of diet on gene expression. There are well-established gene–diet interactions for which specific dietary precautions are necessary, such as phenylketonuria, a genetic disorder requiring a lifetime of a phenylalanine-restricted diet, and so-called lactose intolerance, which is not a disease but a phenotype common to the majority of the world's population (including in the Mediterranean region) who lack a polymorphism upstream of the lactase gene [7]. The effect of the polymorphism, common in central and northern Europe, is to ensure the continued production of the lactase enzyme, which would otherwise cease during childhood.

The application of genetics and genomics to nutritional research is increasing detailed knowledge of metabolic pathways, but an added benefit is that it is bringing more consistency to nutritional research in general. Nutrition research as well as candidate gene-association studies have produced many inconsistent results over the decades, which translates into a level of confusion in the public health message. This is not related to the overall quality of the research; rather, it is because of the complexity of the effects of nutrition on long-term health and confounding due to individual variation. A good example is the association between coffee consumption and myocardial infarction (MI): many years of epidemiological studies yielded inconclusive results, which Cornelis et al. [8] hypothesized may be in part because of a lack of stratification according to caffeine metabolism genotype. Caffeine is metabolized by the enzyme CYP1A2, and a common genetic variation in this gene determines whether an individual metabolized caffeine quickly or slowly. In a study of over 4000 subjects, no significant cardiovascular risk was associated with coffee consumption in the entire study group; however, when stratified, the risk in fast metabolizers did not increase, whereas in the subset of slow metabolizers it increased significantly (odds ratio [OR] of 1.7 for $\geq$4 coffees per day) [8]. The point here is that in even a very large epidemiological study with a relatively simple-to-measure intake, the significant risk in a subsection of the population would not have been revealed, and in smaller studies the results would have been—and indeed were—inconsistent.

The review by Ordovas et al. [6] mentioned above highlighted the status of early nutrigenomics studies in general as well as those with particular application to the Mediterranean diet (MD), and some significant reproducible gene–diet interactions were reported. This area of research has progressed significantly over the past ten years; there is more consistency, and increased numbers of gene–diet interactions, which are reviewed here, have been confirmed. The direct benefit of these studies is the possibility of using the knowledge for modifying nutritional advice for the individual.

NUTRIGENETICS, NUTRIGENOMICS, AND DIET

Nutrigenetics: Use of the MD to Neutralize Potentially Negative Effects of Some Common Genetic Variants

Development of common complex diseases involves multiple genes plus multiple environmental factors, and actual individual risk is determined by gene–environment interactions [9]. In fact "genetic risk" associated single nucleotide polymorphisms (SNPs), such as skin color, have the potential to both increase and decrease risk, depending on the environment.

A well-studied example of this interaction is the C677T SNP in the *MTHFR* gene and acid metabolism, which is important for thymidine synthesis and DNA methylation in pathways that have direct effects on genome stability and homocysteine levels, respectively [10,11]. The 677T allele causes an amino acid change that results in a much lower enzyme activity, having just 30% the activity of the 677C encoded enzyme [12]. In gene–disease association studies the T allele has been associated with increased risk of cardiovascular disease (CVD) [13] but may be protective against some cancers [10]; however, the effects are dependent on the availability of folic acid in the diet. At levels <400 μg/day, 677TT homozygotes are likely to have chronically high levels of homocysteine, which is an independent risk factor for CVD and osteoporosis [14]. With adequate folic acid in the diet, the potential increased risk for CVD and other diseases is neutralized and the protection against some cancers is maintained. Therefore the SNP itself does not increase or decrease any risks—its effects depends on diet.

The geographic distribution of the SNP is interesting from this point of view. The variant T allele is very common in areas where traditional diets have high folic acid content (e.g., southern Europe; ~20-25% of southern Italians are 677TT homozygous), but it is relatively rare in areas where folic acid is low (e.g., northern Europe; in Finland <4% are homozygous) [15–17]. The hypothesis is that the T allele was "allowed" by natural selection to become common in areas with high folic acid because it has protective effects *when* there is adequate folic acid and, vice versa, the prevalence of the SNP was reduced by migrations to northern Europe because of negative selection pressure of low folic acid. This dramatic effect of traditional diets and migration on the geographic prevalence of the C677T SNP is evidence that even single SNPs interacting with diet can have significant long-term health effects. Where nutrigenetic research identifies important gene–environment interactions, it becomes possible to intervene and reduce or neutralize the increased risks associated with particular genetic variants. Some recent studies have demonstrated this in the case of the MD and several potential risk alleles for common diseases.

One of the first formal projects investigating the effects of genetic variation on the response to the MD was the Medi-RIVAGE study [18], which enrolled 212 male and female subjects with at least one cardiovascular risk factor between 1998 and 2002 and compared an MD to a standard low-fat diet. They eventually reported data from 169 subjects who were genotyped for 23 polymorphisms, showing interactions between some genetic variants and reduced cardiovascular risk [19]; although the numbers were small the project provided some early evidence of individual differences in response to the MD. Recent work in larger studies has reproducibly identified several gene-environment interactions relevant for components of the MD (Table 1).

The *FTO* gene has been repeatedly associated with obesity in many different cohorts, and it is accepted as the gene most strongly associated with obesity (although of course it is still only one of many involved genes and its effect is small). Subsequent studies have suggested that the increased risk is dependent on diet and lifestyle, including levels of specific macronutrients such as saturated fats [21]. Moleres et al. [32] looked at the effects of fatty acids in 354 Spanish children and reported that the increased risk for obesity associated with the A allele (of the *FTO* rs9939609 polymorphism) was seen only when saturated fatty acid (SFA) consumption was high (>12.6% of total energy) and/or when the polyunsaturated fatty acid (PUFA) consumption was relatively low (PUFA-to-SFA ratio <0.43%); thus increasing PUFAs and reducing SFAs had the effect of neutralizing the risk associated with the allele and reducing odds of risk of obesity threefold. These and other data clearly show that the *FTO* genetic variant does not in itself increase the risk of obesity; it does so only under certain dietary conditions.

The *PPARγ* (peroxisome proliferator-activated receptor γ) gene contains a polymorphism that changes the amino acid at position 12 in the protein from proline to alanine. PPARγ is a transcription factor that is involved in glucose and lipid homeostasis. In association studies the Pro12 allele has been linked with a small increased risk in type 2 diabetes mellitus (T2DM) whereas the Ala12 is slightly protective [33]; on the other hand, depending on the type of diet, the Ala12 allele has been associated with increased weight gain [34,35]. Several studies of the MD have looked at the effects according to *PPARγ* genotype. In 2009 Razquin et al. [20] published results of a 2-year intervention study of 774 patients at high risk of CVD in the PREDIMED randomized trial, which aimed at assessing the effect of the MD on CVD prevention.

TABLE 1 Examples of Gene—Mediterranean Diet (MD) Interactions (See Text for Details)

Phenotype	Gene–Diet Interaction	Effect	References
MD versus Western-type diets			
Weight gain	*PPARγ* MD versus control diet	Reduced increase in waist circumference among Ala allele carriers in the MD group (>2-cm difference)	[20]
Obesity risk	*FTO* Saturated fats PUFAs	Increased obesity risk only when saturated fat (SFA) consumption was high (>12.6% total energy) and/or when PUFA consumption was relatively low	[21]
	PPARγ *FTO* Carbohydrates and physical activity	Higher obesity risk in Ala allele (*PPARγ*) and A allele (*FTO*) carriers with high intake of refined carbohydrates and sedentary lifestyle	[22]
	ADIPOQ *IL6* MD versus control diet	Reduced risk for obesity in MD with high intake of olive oil and/or nuts	[23] [24]
T2DM	*FTO* *MC4R* MD versus non-MD diets	When adherence to the MD was low, carriers of the variant alleles had higher risk for T2DM	[25]
	Various (10 SNPs, genetic risk score) "Prudent" (e.g., MD) versus Western diet	With a high genetic risk score, those following the "prudent" diet had low odds of developing diabetes (OR 0.9–1.0), whereas those with the worst combination of high genetic risk score + Western diet were at an almost three times increased risk	[26]
Individual differences in the response to the MD			
Weight loss	Various (24 variants) Nutrigenetic versus normal diet	Nutrigenetically enhanced traditional MD was more effective at improving risk biomarker profiles (glucose, LDL, homocysteine) and long-term weight loss	[27]
	CLOCK Reduced-calorie MD	Individuals with the G allele lost less weight than subjects with the more common AA genotype The minor allele carriers also had significantly higher ghrelin levels	[28] [29]
BMI	*APOA2* Saturated fats	The CC genotype (15% of the populations) was associated with a 6.8% greater BMI in those consuming a diet high, but not a low, in saturated fat	[30]
Lipid profile	*APOA5* Saturated fats	Carriers of the minor allele were somewhat protected against higher BMI and triglyceride levels associated with a higher-fat diet	[31]

BMI, body mass index; LDL, low-density lipoprotein; OR, odds ratio; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; SNP, single nucleotide polymorphism; T2DM, type 2 diabetes mellitus.

Two groups followed an MD and the control group a standard low-fat diet. Over the course of the study, in the control group there was a higher change in waist circumference (>2 cm) in carriers of the Ala allele, but this was not seen in the MD groups, and there was a greater beneficial effect seen in patients with T2DM. This suggests that the Ala allele may be protective against T2DM but only under the right diet and lifestyle conditions (e.g., a Mediterranean-type diet); otherwise it can be negative. In another study of 978 elderly Spanish subjects, Galbete et al. [22] observed a higher risk of obesity in subjects with the Ala12 allele who were inactive or had a high carbohydrate intake (>246 g/day), and the risk was further increased in the presence of the *FTO* minor allele (rs9939609). The extensive data for these two genes may help to explain why, as shown by Elhayany et al. [36], a low-carbohydrate MD was more effective at reducing CVD and T2DM risk factors than the standard American Diabetic Association-recommended diet.

Another gene associated with increased risk of obesity (and metabolic syndrome) is adiponectin. Raquin et al. [23] investigated the effect of a 3-year intervention with a Mediterranean-style diet in 737 overweight individuals with a high cardiovascular risk. The subjects were assigned to a low-fat diet or to one of two variant MDs: one with a high intake of virgin olive oil and another with a high intake of nuts. They reported that both MDs reversed the increased body weight gain associated with the higher risk adiponectin (ADIPOQ) risk alleles. In a related study the same group also observed that the

MD neutralized the effects of another variant in the interleukin-6 gene: the minor C allele was associated with increased adiposity, but carriers of this allele had the greatest reduction in body weight when following one of the MDs compared to the control diet [24].

Obesity is closely linked to T2DM, so it is not surprising that the same genes are associated with increased risk for both conditions. Both the *FTO* and melanocortin-4 receptor (*MC4R*) genes have been consistently associated with obesity risk and may also be linked to T2DM. In a very large case-control study of 7052 subjects with high cardiovascular risk (50% of whom were diabetics), Ortega-Azorin et al. [25] found that when adherence to MD was low, the carriers of the variant alleles (risk alleles for high body mass index [BMI]) had an increased risk of T2DM (OR 1.21) that disappeared when adherence was high (OR 0.97), and the gene-diet interactions were independent of BMI, suggesting a direct effect on T2DM risk. In the same study group the risk alleles also were found to be neutralized by increased physical activity [37].

As discussed above, common diseases have multiple components, including multiple genetic variants, that contribute to the development of the disease. The study of single gene-diet interactions will increase knowledge of the mechanisms involved but will address only one small aspect of the overall causation. A strategy for simultaneously assessing the overall effects of several genes is to calculate a "genetic predisposition score." In a recent study Qi et al. [26] looked at 10 SNPs associated with T2DM and the effect of diet on the combined genetic score related risk. While they did not look specifically at the MD they showed that a "prudent" dietary pattern (high intake of vegetables, fruit, legumes, whole grains, fish, and poultry) abolished the significant T2DM risk seen in individuals who had a high genetic risk score and consumed a Western-type diet pattern (high intake of processed meat, red meat, butter, high-fat dairy products, eggs, and refined grains). Even with a high genetic risk score, those following the prudent diet had low odds of developing diabetes (OR 0.9–1.0), whereas the worst combination of high genetic risk score plus Western diet were at an almost a three times increased risk.

In summary, there has been a great deal of consistency in studies analyzing genetic risk in the context of diet—in stark contrast to earlier genetic studies that looked at genetic association with disease without taking into consideration diet or lifestyle (in such studies inconsistency was the norm) [38]—and they clearly indicate that the effects of genetic risk alleles can be completely neutralized by specific dietary interventions; adherence to the MD seems to be particularly effective in counterbalancing genetic risk associated with the major complex diseases of the present age. Thus, even individuals with a high *genetic* risk for a common disease do not necessarily have a high *actual* risk; in fact, depending on diet and lifestyle, the overall risk can be reduced to significantly below average.

Nutrigenetics: Individual Differences in Response to the MD

The previous section looked at how the MD can be used to counteract the potentially negative effects of particular genetic variants. This section looks at further personalization of the MD itself. Just as one size does not fit all, so one MD does not fit all, and there is evidence that some aspects of the MD can be beneficially modified when certain genetic variants are present.

The first evidence of this appeared in a study reporting the use of nutrigenetics in clinical practice that was published in 2007 [27], the subject of which was long-term weight loss; a total of 93 patients with a history of poor weight control were treated with a traditional MD; in the control group the MD was modified for each individual according to phenotypic and lifestyle parameters (e.g., food preferences, age, sex, BMI, activity levels), and the diets of the nutrigenetic group were further personalized according to genetic variation (among a panel of 24 genetic variants). The data reported showed that the nutrigenetically enhanced traditional MD was more effective at improving risk biomarker profiles (glucose, low-density lipoprotein, homocysteine) and long-term weight loss. After 12 months the majority of the control group had regained weight, whereas the nutrigenetic group did not, and the probability of maintaining weight loss over the long term was six-times higher in the nutrigenetic group (OR 6.1).

Several more recent studies that demonstrate specific effects of individual genes on the response to Mediterranean-type diets have been published. The *CLOCK* gene is involved in control of the circadian rhythm and can have an influence on the response to weight-loss diets. Garaulet et al. [28] reported that the *CLOCK* rs1801260 SNP may predict the outcome of body weight reduction strategies based on reduced-calorie Mediterranean-type diets. They looked at 500 subjects who were prescribed a 28-week reduced-calorie MD and found that over this period individuals with the G allele lost less weight than subjects with the more common AA genotype (7.96 vs. 10.41 kg over 28 weeks). Another study by the same group showed similar results in a separate cohort of 1495 overweight subjects; the minor allele carriers were more resistant to weight loss, and the rate of loss slowed significantly, after 12 weeks. The minor allele carriers also had significantly higher ghrelin levels and they ate at different times (e.g., ate late breakfasts and more in the evening); there also was less compliance to the MD (with higher intake of processed foods and trans fatty acids). The minor allele carriers also slept less, which itself has been

associated with increased BMI [29]. A separate study by a different group suggested that more intense physical activity can be beneficial for weight loss in the presence of the minor allele [39]. Taken together, these interesting studies suggest that carriers of the *CLOCK* minor allele who are seeking to lose weight may not respond to a typical MD and require specific education about eating habits, exercise, and compliance if they are to achieve optimum results.

The *APOA2* gene codes for apolipoprotein 2, which is the second most abundant protein of the high-density lipoprotein particles, but its function remains largely unknown [40]. The interaction of this gene with diet, particularly saturated fats, has been well studied and results have been reproduced in several thousand subjects from six different populations. Corella et al. [30] analyzed gene–diet interactions between the APOA2-265T > C polymorphism and saturated fat intake (<22 or ≥22 g/day). In Mediterranean individuals, the CC genotype (∼15% of the population) was associated with a 6.8% greater BMI in those consuming a high-fat diet, but not a diet with low saturated fat. While the MD is naturally low in saturated fats, carriers of the CC allele apparently need to be particularly careful of saturated fat content to either lose weight or reduce the risk of weight gain.

Genetic variability at the *APOA5* locus also has been associated with increased CVD risk; however, the macronutrient content of the MD may affect this risk. An association was found between the APOA5-1131T > C SNP and fat intake; apparently carriers of the minor allele were somewhat protected against higher BMI and triglyceride levels associated with a higher fat diet [31].

These examples illustrate that genetic variation can influence the effects of the MD in different individuals. This line of research is growing rapidly and will no doubt yield further information that may be useful in making the MD even more effective at the individual level.

Nutrigenomics: Investigating the Effect of the MD on Gene Expression

Many studies have demonstrated that adherence to the MD leads to improvement in levels of biomarkers associated with inflammation and oxidative stress, which may explain, at least in part, the diet's association with reduced risk for CVD [41]. The mechanisms for these actions of the MD have been the subject of recent nutrigenomics research. While genotype affects response to nutrients (metabolism, transport, excretion, etc.), as discussed in the previous sections, certain nutrients also have an effect on our genes, altering their expression in a specific and targeted manner. Diet also affects the level of many circulating metabolites, and recent technology developments allow the simultaneous detection of thousands of metabolic pathway intermediates; transcriptomics, proteomics, and metabolomics have been used to dissect the mechanisms responsible for the apparent benefits of the MD.

The effects of certain critical ingredients of the MD on gene expression and on various metabolite levels have been investigated. Most work has looked at the effect of lipids, including monounsaturated fatty acids (MUFAs) present in olive oil and omega-3 PUFAs in fish and nuts. The first nutrigenomics studies of humans to be published appeared in 2009; they investigated the effects of PUFAs, MUFAs, and SFAs. These were single-blind crossover studies of 21 healthy men; peripheral blood mononuclear cells were isolated 6 hours after the intervention and the whole-genome expression was profiled. The study compared gene expression following a drink containing 55 g test fatty acids (65% PUFAs vs. 80% MUFAs vs. 70% SFAs). PUFAs led to upregulation of 225 genes and downregulation of 212 genes, and SFA upregulated and downregulated 196 and 101 genes, respectively. The studies showed that the main expression changes were associated with processes related to liver X receptor signaling, oxidative stress, inflammation, carbohydrate metabolism, and a variety of other processes, and the effects of PUFAs were the opposite of SFAs [42]. A separate double-blind clinical trial of elderly subjects using a 26-week intervention with fish oil containing a low or high dose of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) (0.4 vs. 1.8 g, respectively) reported that high EPA + DHA changed the expression of 1040 genes compared with the control (high dose of oleic sunflower oil), which changed the expression of only 298 genes. Interestingly, EPA + DHA intake led to reduced expression of genes involved in inflammatory- and atherogenic-related pathways, such as nuclear transcription factor B signaling, eicosanoid synthesis, scavenger receptor activity, adipogenesis, and hypoxia signaling. The overall changes demonstrated that the 6-month intake of EPA + DHA led to a more anti-inflammatory and anti-atherogenic gene expression profile [43].

Olive oil is a key ingredient of the MD and, when it has a high phenol content, has been shown to reduce inflammation, oxidative stress, and prothrombotic markers. The effects of the phenolic component of olive oil on the expression of over 30,000 genes was studied in blood mononuclear cells following a virgin olive oil-based breakfast with high (398 ppm) and low (70 ppm) content of phenolic compounds in 20 patients with metabolic syndrome. The analysis identified 98 genes whose expression was altered by the high phenolic content (79 underexpressed and 19 overexpressed), and many were linked to metabolic syndrome pathways; the reduced expression of several proinflammatory genes was observed [44].

TABLE 2 Nutrigenomics: The Effect of the Mediterranean Diet on Gene Expression

Phenotype	Dietary Components	Effect	References
Inflammation Oxidative stress	Saturated fats (SFAs) MUFAs PUFAs	PUFAs led to upregulation of 225 genes and downregulation of 212 genes and SFA up- and downregulated 196 and 101 genes, respectively PUFAs had (beneficial) effects on expression opposite to those of SFAs	[42]
Inflammation	Fish oil (EPA and DHA)	EPA + DHA intake led to reduced expression of genes involved in inflammatory- and atherogenic-related pathways	[43]
Inflammation	Olive oil (high vs. low phenols)	Reduced expression of several proinflammatory genes was observed	[44]
Inflammation Oxidative stress	Olive oil (high vs. low phenols)	Decreased oxidative and inflammatory plasma markers Modified expression of genes involved in inflammation and oxidative stress, with enhanced effects seen in the high polyphenol group	[45]

EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid.

In a separate controlled clinical trial of 90 healthy volunteers, a separate group measured the effects of a traditional MD with virgin olive oil or with washed olive oil (i.e., reduced phenolic content). Compared with a control diet, both of the MDs decreased oxidative and inflammatory plasma markers and affected the expression of genes involved in inflammation and oxidative stress; enhanced effects were seen in the high polyphenol group, and the authors concluded that the olive oil polyphenols had a significant role in the downregulation of proatherogenic genes in the context of a traditional Mediterranean diet [45] (Table 2). A recent review of the literature on the transcriptomic effects of the MD in humans confirmed the several lines of evidence that changes in gene expression in oxidative stress, inflammation, and atherogenic markers (such as tumor necrosis factor and interferon-γ) is one mechanism of the MD effect [46]. These are interesting results from initial studies: the review concluded that "data in this field, although scarce, are promising"; progress is challenging because of the intensive nature of these types of investigations, which require highly controlled dietary interventions followed by detailed analysis of thousands of genes or metabolites. However, over the next few years researchers are likely to uncover many of the specific health-promoting pathways that are stimulated by components of the MD.

CONCLUSIONS

Over 50% of the adult population in the European Union is overweight or obese; levels have tripled over the past 20 years, and the trend shows no sign of slowing. The consequential serious social and economic problems are further compounded by the earlier onset of these diseases, causing, in addition to personal suffering, significant loss of work-years and a drain on resources [47]. Against this background, the MD is understandably receiving renewed attention by researchers and health care practitioners alike.

During the twentieth century, great progress in improving health care was made. Notable successes include the eradication, at least in Europe, of most diseases of malnutrition; protection against infection through vaccination and antibiotics; and effective public health efforts against smoking. Over the past 50 years, however, rapid technological progress has been accompanied by (and has contributed to) negative effects on diet and lifestyle—the two most important factors in the cause of chronic disease. Our environment has changed enormously, leading to increased food choice and availability, along with the desire and, at least in part, the necessity for reduced costs accompanied by lower quality; we consume far more sugar and processed foods, and intensive agriculture has reduced the nutrient content of many vegetables [48–50]. In addition, developments in transport and technology have reduced the time we spend being physically active, resulting in an increased sedentary lifestyle. Also, in the face of this, the public health message has to combat ever more intense and creative commercial efforts to sell unhealthy foods and products. The resulting environment has become more "obesogenic" and "diseaseogenic."

The nutrigenetic and nutrigenomic studies presented in this chapter support the proposal by Ordovas and colleagues that the health benefits associated with the traditional MD may have genetic roots—that our genetic background evolved to work optimally with the MD and lifestyle. The answer to our health problems is "simple": we should combine the healthier aspects of earlier decades while maintaining beneficial progress of the current era. Of course, the answer is not so simple:

(1) the public health message is either not heard, not understood, or is ignored, and (2) it does not meet the needs of the individual. In fact, the public health approach is somewhat paradoxical [51]; it is aimed at the majority who are at moderate individual risk rather than the individuals at highest risk because "a large number of persons with moderately increased risk levels contribute more cases than a small number with extreme risk levels." This dilutes the effect of the message to each individual, making it seem impersonal, less relevant "for me," and therefore often ignored. A more individualized approach also is required because, as the studies presented in this chapter demonstrate, genetic variation influences response to diet, and while a general MD may be healthy for the population, a personalized MD will be more healthy for the individual.

The MD is not expected to be the panacea for all of the growing lifestyle-related health problems facing the Western world; indeed, there are some who argue that rather than focusing on a single regional diet it may be more appropriate to promote healthy nutritional aspects of local diets for different populations [52]. How much of the benefits are related to the Mediterranean lifestyle itself? [53]. Should the Scandinavian population follow the Mediterranean or the Nordic diet? [54]. These are good questions. Nutrigenetics and nutrigenomics are unlikely to be able to determine which individual will respond best to which diet; nutrition and genetics are too complex to expect, or promise, such simplistic answers. The benefits of nutritional genetics will most likely be found in the fine tuning of generally healthy diets and certainly in improving the reliability and consistency of all nutritional research.

The concept of personalized nutrition is not new, but the application of nutrigenetics now—and eventually nutrigenomics—is making it a growing reality. There is still a healthy debate about how much can be achieved with nutrigenetics [55], but there is good evidence that it can be beneficial, and there is little doubt that this knowledge may provide the basis for successful public health as well individual approaches for disease prevention [6].

SUMMARY POINTS

- Nutrigenetics studies common genetic variants (usually SNPs) that affect the activity of proteins involved in the assimilation, transport, and metabolism of dietary nutrients.
- Nutrigenomics studies the direct or indirect effects nutrients can have on gene expression.
- Gene–diet interactions have a strong influence on long-term health, especially in the development of the common complex diseases of aging (e.g., CVD, T2DM).
- In Western society these common diseases are becoming more prevalent at an earlier age, affecting personal, social, and economic well-being.
- The MD has been shown to be effective at reducing risk factors associated with certain genetic variations interacting with a nonoptimal nutrition.
- The MD itself is also not "one size fits all," and there is evidence that it can be optimized for the individual by making specific modifications according to genotype.
- Components of the MD (especially MUFAs and PUFAs from olive oil, fish, and nuts) have been demonstrated to have a positive effect on the expression of genes involved in inflammation and oxidative stress.

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