Proceedings of the Nutrition Society (2004), **63**, 145–152 DOI:10.1079/PNS2003313
© The Author 2004

The Summer Meeting of the Nutrition Society was held at King's College, London on 7–10 July 2003

Symposium on 'New sights into variability in lipid requirements'

The quest for cardiovascular health in the genomic era: nutrigenetics and plasma lipoproteins

Jose M. Ordovas
Nutrition and Genomics Laboratory, JM-USDA-Human Nutrition Research Center on Aging at Tufts University, Boston, MA 02111, USA

Nutrigenetics and nutrigenomics are promising multidisciplinary fields that focus on studying the interactions between nutritional factors, genetic factors and health outcomes. Their goal is to achieve more efficient individual dietary intervention strategies aimed at preventing disease, improving quality of life and achieving healthy aging. Our studies, and those of many other investigators, using population-based and intervention studies have found evidence for interactions between dietary factors, genetic variants and biochemical markers of CVD. Now, the characterization of individuals who may respond better to one type of dietary recommendation than another can be begun. Thus, a low-fat low-cholesterol strategy may be particularly efficacious in lowering the plasma cholesterol levels of those subjects carrying the apoE4 allele at the *APOE* gene. HDL-cholesterol (HDL-C) levels are also modulated by dietary, behavioural and genetic factors. It has been reported that the effect of PUFA intake on HDL-C concentrations is modulated by an APOA1 genetic polymorphism. Thus, subjects carrying the A allele at the –75 G/A polymorphism show an increase in HDL-C with increased intakes of PUFA, whereas those homozygotes for the more common G allele have the expected lowering of HDL-C levels with increased intake of PUFA. Variability at the hepatic lipase gene is also associated with interactions between intake of fat and HDL-C concentrations that could shed some light on the different abilities of certain ethnic groups to adapt to new nutritional environments. This knowledge should lead to successful dietary recommendations partly based on genetic factors that may help to reduce cardiovascular risk more efficiently than the current universal recommendations.

Nutrigenetics: Cardiovascular health: Plasma lipoproteins

The 'graying' population and its health and societal consequences

The World is 'growing older.' About 19% of the populations of developed countries are >60 years of age, whereas only 50 years ago the corresponding level was only 8%. Current predictions estimate that by the year 2050 the 'over-sixty' population will represent more than double the current levels (Tinker, 2002). Physiological decline is considered to be the normal path to old age. To account for this ingrained concept, the World Health Organization (2000) has established scores based on the disability-adjusted life expectancy indicator, which subtracts the years of ill health from the overall life expectancy to give the equivalent years of healthy life. According to this indicator, Americans spend relatively more of their life ill or disabled and die earlier than populations from similarly advanced countries, thereby heavily taxing health care resources (Birmingham, 2000). However, the increasing frailty that is termed senescence may not be the obligated fate of the aging individual (Kirkwood, 2002). The complete elimination of the aging-related decline may be complete utopia; however, there is general optimism that major advances can be made in reducing the gap

Abbreviations: HDL-C, HDL-cholesterol; T2DM, type 2 diabetes mellitus.

Corresponding author: Professor J. M. Ordovas, fax +1 617 556 3211, email jordov01@tufts.edu

https://doi.org/10.1079/PNS2003313 Published online by Cambridge University Press

between 'normal' aging and ideal aging. There is no doubt that the best approach to achieving the road to 'healthy aging' starts with disease prevention. To do so, action is needed early in life and solid scientific evidence must be presented to support the chosen recommendations and actions.

The major causes of morbidity and mortality in the USA and in most other developed countries are CVD. The incidence of CVD has experienced a dramatic evolution during the last 100 years. In the early 20th century CVD was described as 'a rare disease in hospitals: a case a month was the average, even in large metropolitan hospitals' (McCrae, 1912). Nowadays, according to the World Health Organization (2002), CVD accounts for $>12 \times 10^6$ deaths worldwide each year. The sudden emergence of CVD as a major public health concern during the 1940s fostered research towards understanding the factors determining this disease. Thus, projects like the Framingham Heart Study were launched to identify CVD 'risk factors' (Dawber *et al*. 1951). Focus during the early years was placed on the identification of biochemical, environmental and behavioural risk factors. During the last few decades several CVD risk factors were well established, and they are commonly used for the detection and treatment of subjects at risk. However, CVD is a complex disorder and the battle against it is far from complete. This complexity is evident from the fact that after so many years of intense research, and accumulation of knowledge about risk factors, there is still only partial understanding of the molecular mechanisms leading to atherosclerosis and to CVD.

CVD are the paradigm of multifactorial disorders encompassing multiple genetic and modifiable risk factors. The current recommendations aim to reduce the modifiable risk factors, and much emphasis has been placed on controlling high plasma cholesterol levels. However, this variable is just one of a constellation of risk factors associated with CVD. The most common cluster of these risks is known as the metabolic syndrome, which is characterized by the concurrence of obesity, dyslipidaemia, hyperglycaemia and hypertension. The dramatic increase in CVD risk associated with this syndrome has brought to it a graphic and self-explanatory definition, 'the Deadly Quartet' (Brotman & Girod, 2002; Mandell, 2002; Nambi *et al*. 2002).

The impact of the metabolic syndrome on the quality of life and health care costs in the USA is appalling. The most current estimates indicate that 24% of the population who are ≥20 years are affected. However, underneath this global statistic hides even more alarming information. First, there is considerable heterogeneity among ethnic groups, with Hispanic populations withstanding the worst of the problem, probably as a result of a combination of gene and environmental interactions. Moreover, the impact on the elderly is even more terrifying, with 40% of individuals who are >60 years of age affected by this disorder. If major advances are to be made against this major killer, it is necessary to understand the molecular mechanisms responsible for the metabolic abnormalities and how these four apparently distinct conditions (obesity, dyslipidaemia, hyperglycaemia, and hypertension) may arise from a common pathophysiological process. In other words, it is necessary to identify the conductor of 'the Deadly Quartet' (Mandell, 2002).

The expression of the metabolic syndrome, like that of CVD, involves genetic and environmental factors. In order to move forward with the elucidation of the genetic component, our understanding of the genetic basis for each of its components (energy balance, lipid homeostasis, insulin resistance and high blood pressure) must be advanced. The following is a summary of our knowledge of the genetics underpinning each of these metabolic disarrangements.

Plasma lipids: the first of many risk factors

The link between serum cholesterol and the development of atherosclerosis has been well established. The National Cholesterol Education Program Adult Treatment Panel III (2002) published updated guidelines for the treatment of lipid disorders, greatly expanding the number of subjects eligible for therapy. According to the current cut-off points for plasma lipid and lipoprotein concentrations, the number of adults in the USA who need therapeutic lifestyle changes is estimated at 65 million. In the new recommendations several important changes have been made in the identification and management of subjects at risk for CHD. Although the National Cholesterol Education Program Adult Treatment Panel III (2002) maintains that LDL-cholesterol should be the primary target of lipid-lowering therapy, it identifies non-HDL-cholesterol (HDL-C) as a secondary target in patients with elevated triacylglycerols. Subjects with two or more CHD risk factors should now be assessed for 10-year absolute CHD risk based on the Framingham Point Scale (Wilson *et al*. 1998) in order to identify those individuals who require more aggressive treatment. The guidelines also designate a new category, CHD risk equivalent, which recognizes that certain subjects have the same high risk as those with established CHD. Diabetes is now identified as a CHD risk equivalent, and increased emphasis is placed on the already described constellation of metabolic risk factors known as the metabolic syndrome. The National Cholesterol Education Program Adult Treatment Panel III (2002) continues focusing on dietary modification as the cornerstone of primary prevention, with emphasis on reduction of the high-saturated-fat atherogenic diet, obesity and sedentary lifestyle. However, the general recommendations do not take into account the well-known fact that individuals display a very wide range of responses to any therapeutic intervention, and it is not known how many individuals can achieve the recommended levels of serum lipids using the generally recommended approaches. The major reason for this uncertainty is that although there are algorithms for predicting plasma cholesterol response to changes in dietary fat and cholesterol in groups of individuals, it is not possible at this time to predict the response of the individual.

It should be emphasized that the relationships between dietary changes and serum lipid changes for groups are well founded and predictable; however, because of the striking variability between subjects in the response of serum cholesterol to diet it is not possible to predict the

https://doi.org/10.1079/PNS2003313 Published online by Cambridge University Press

individual response. It has been shown already in studies with non-human primates that the serum lipoprotein response to dietary manipulation has an important genetic component (Mahaney *et al*. 1999; Rainwater *et al*. 1999, 2002*a*,*b*; Baroukh *et al*. 2001). Such genetic variability could have a marked impact on the success of public health policies and those of the National Cholesterol Education Program Adult Treatment Panel III (2002). Furthermore, the summary of a Scientific Conference on Preventive Nutrition: Pediatrics to Geriatrics convened by The Nutrition Committee of the American Heart Association (Deckelbaum *et al*. 1999), specifically concluded that 'theoretically, genetic differences can render a particular set of dietary conditions more harmful or beneficial in one ethnic group than in another. This is one explanation for why individuals of different ethnic groups who consume similar diets might have varying disease profiles.' Moreover, the statement emphasized the need to 'identify specific genes and genetic variations that affect risk directly and indirectly by the way they interact with nutrients.'

Lipoproteins are macromolecular complexes of lipids and proteins that originate mainly from the liver and intestine, and are involved in the transport and redistribution of lipids in the body. Lipid and lipoprotein metabolism can be viewed as a complex biological pathway containing multiple steps. Lipid homeostasis is achieved by the coordinated action of a large number of nuclear factors, binding proteins, apoenzymes and receptors. Lipid metabolism is also closely linked with energy metabolism and is subjected to many hormonal controls that are essential for adjustment to environmental and internal conditions. Genetic variability has been found in man for most of these components regulating plasma lipid levels. The challenge has been to find which ones and how many of those variants will be required to be able to forecast CVD risk and to provide successful recommendations. Judging from the current status of the field, this challenge will continue for years to come.

Non-insulin-dependent diabetes mellitus: the tip of the iceberg for insulin resistance

The temporal and geographical variation in the prevalence of type 2 diabetes mellitus (T2DM) is quite dramatic. Its global prevalence has increased exponentially over the last few decades. In 1995 it was estimated at 135 million; 20 years from now, it is expected to increase to >300 million. The geographical pattern of variation suggests that prevalence is lowest in rural areas of developing countries, is generally intermediate in developed countries, but is highest in certain ethnic groups who have adopted Western lifestyle patterns. The thrifty genotype hypothesis speculates that a genetic predisposition to obesity and diabetes would be advantageous in times of food scarcity, as it would promote efficient retention of energy stores, but would become disadvantageous in the current times of relative food abundance and low energy expenditure (Wareham *et al*. 2002; Abate & Chandalia, 2003; Meigs, 2003; Quinn, 2003). The importance of genetic factors for T2DM has been demonstrated by studies of familial aggregation, high concordance in twin studies and the impact of different extents of high-risk heritage on diabetes risk in high-prevalence populations like the Pima Indians (Ravussin & Bogardus, 2000). Strong evidence is also available to suggest that quantitative traits underlying diabetes have a major genetic component, with familial aggregation of hyperinsulinaemia and hyperglycaemia. It has been estimated that 20–25% of the variance in fasting insulin levels and about 50% of the variance in fasting glucose levels could be attributed to genetic factors, while the remainder of the variance could be attributed to unique environmental factors. Although the weight of evidence supporting a genetic aetiology is considerable, identifying the specific genetic factors responsible has proved much more difficult (Cox, 2002; Mercado *et al*. 2002; Gloyn, 2003).

Monogenic forms of diabetes may account for perhaps 1 or 2% of all cases of diabetes. One of the main approaches used for the identification of genetic factors in T2DM has been the use of genome-wide scans within collections of families with diabetes. To date, although various 'hot' areas of linkage have been found in several of the scans (such as on chromosomes 20, 12, and 1), the only example of a specific gene detected by this approach is calpain 10, which was found in an area on chromosome 2 previously demonstrated as a likely site by linkage in a genome-wide scan in Mexican Americans (Cox, 2002).

An alternative and simpler approach does not involve family-based collections or linkage, relying instead on the quantification of the association between genetic variants and diabetes using the case–control approach. A clear limitation of this approach is that it is restricted by knowledge of potential genetic candidates. As with all case–control studies, the other principal issues relate to questions of selection bias, adequacy of control populations and power. Studies examining the association of common polygenes for T2DM will need to be powered to detect small increases in risk. However, another strategy could involve the use of populations enriched in the clinical outcome, or alternatively on the metabolic precursor of the disease, i.e. insulin resistance.

In addition to the presence of genetic predisposition, the overall importance of environmental factors is demonstrated by observations of increased diabetes risk among individuals from at-risk populations who migrate to countries in which lifestyles are more Westernized (Wareham *et al*. 2002; Abate & Chandalia, 2003; Quinn, 2003). Even stronger evidence has emerged from cohort studies in which the importance of major non-genetic risk factors such as obesity, physical inactivity and dietary intake of fat have been clearly demonstrated. The same pattern of association with environmental factors is demonstrable in cross-sectional studies in which the outcome variable is not diabetes risk but one of the quantitative metabolic traits that are associated with diabetes (for a comprehensive review, see Wareham *et al*. 2002). These traits include those on which the diagnosis of diabetes is based (fasting and 2 h post-glucose load glucose levels) and other related continuously distributed measures of hyperglycaemia (glycated Hb A_1) and surrogate markers of insulin resistance, such as the fasting insulin concentration. The strength of causal inference in relation to these aetiological

https://doi.org/10.1079/PNS2003313 Published online by Cambridge University Press

factors is high, not only because findings have been replicated in many studies in different populations, but also because interventions aimed at changing these factors have led to reductions in the incidence of diabetes in randomized controlled trials, demonstrating that T2DM is a largely preventable disease. Furthermore, two recent intervention studies have confirmed the value of lifestyle changes in the prevention of T2DM. The first was the Finnish Diabetes Prevention Study (Tuomilehto *et al*. 2001), which examined whether the onset of T2DM could be prevented through lifestyle modification in subjects with impaired glucose tolerance. In this study subjects were assigned to either an intervention group or a control group. Subjects in the intervention group received individualized counselling aimed at weight reduction, dietary fat reduction, saturated fat reduction, increased dietary fibre and increased physical activity. The mean duration of the follow-up was 3·2 years. The risk of T2DM was reduced by 58% in the intervention group, and the reduction in the incidence of T2DM was directly associated with changes in lifestyle. In the second study, the Diabetes Prevention Program (The Diabetes Prevention Program Research Group, 2000; Hernan *et al*. 2003), 3234 adults with elevated fasting and post-load plasma glucose concentrations were randomized to a placebo, metformin (850 mg twice daily) or a lifestyle modification programme with goals of at least a 7% weight loss and 150 min physical activity per week. The average follow-up was 2·8 years, and the incidence of T2DM was 11·0, 7·8 and 4·8 cases per 100 person-years in the placebo, metformin and lifestyle groups respectively. Lifestyle intervention reduced the incidence by 58% and metformin reduced it by 31% as compared with the placebo. In order to prevent one case of diabetes during a 3-year period 6·9 subjects would have to participate in the lifestyle intervention programme and 13·9 would have to receive metformin. Hence, lifestyle intervention was more effective than metformin treatment.

The evidence, therefore, that genetic and environmental factors are both important in the aetiology of diabetes is strong (Hanson & Knowler, 2003; McCarthy, 2003), as is the concept that primary prevention focusing on insulin resistance is the most economic and successful approach for reducing the current epidemic of diabetes and the subsequent risk of CVD. This approach will require adequate early warning signals such as informative genetic markers, which are currently lacking.

Obesity: the chicken or the egg of the metabolic syndrome

The most recent data on the epidemic of obesity and overweight in the USA (US Department of Health and Human Services, 2001) are alarming; of US adults, 34% are considered overweight and an additional 31% are obese. The consequences of this situation are far beyond the aesthetics of the population. Obesity-related causes are responsible for the deaths of 300 000 individuals per year, thus making it the second-leading cause of death after smoking. Being overweight or obese increases the risk of hypertension, heart disease, stroke, diabetes and some cancers. Americans spend >US $\$33 \times 10^9$/year on weight-loss products and services. However, the economic cost of obesity in the USA was about US $\$117 \times 10^9$ in 2000. Future trends are even more dreadful, particularly as 15% of youngsters aged 6–19 years and 10% of children aged 2–5 years are considered to be seriously overweight. According to a recent US Surgeon General's call to action (US Department of Health and Human Services, 2001), the 'health problems resulting from overweight and obesity could reverse many of the health gains achieved in the USA in recent decades'. The US Human and Health Services Secretary Tommy G. Thomson reinforced the urgency of this statement, by stating that 'overweight and obesity are among the most pressing new health challenges we face today' (US Department of Health and Human Services, 2001).

The American population is partially aware of the problem, and the solution is apparently very simple, eat less and exercise more. About 45% of women and 25% of men are trying to lose weight at any one time; however, the rates of success are extremely poor. This situation is a clear indication that more targeted and personalized messages are needed. To achieve that goal more research is urgently needed in order to help understand the complex molecular mechanisms involved in energy balance. It is well recognized that genetics play a role that is as important as behaviour in determining individual body weight. However, the picture of the genetics of obesity remains very fragmented and limited. The recently published ninth update of the human obesity gene map (Chagnon *et al*. 2003) is based on evidence from cases of obesity associated with a single gene mutation, Mendelian disorders exhibiting obesity as a clinical feature, quantitative trait loci from human genome-wide scans and various animal cross-breeding experiments, and association and linkage studies with candidate genes and other markers. Evidence of the genetic basis for obesity has been derived from transgenic and knock-out murine models exhibiting obesity (*n* 38; Chagnon *et al*. 2003). Moreover, thirty-three Mendelian syndromes relevant to human obesity have been mapped to a genomic region, and the causal genes or strong candidates have been identified for twenty-three of these syndromes. There are currently 168 quantitative trait loci reported from animal models, and sixty-eight human quantitative trait loci for obesity phenotypes from genome-wide scans. Additionally, linkage peaks with candidate genes have been identified in targeted studies. Seven genomic regions harbour quantitative trait loci replicated among two to five studies. Attempts to relate DNA sequence variation in specific genes to obesity phenotypes continue to grow, with 222 studies reporting positive associations with seventy-one candidate genes. Fifteen such candidate genes are supported by at least five positive studies. The obesity gene map shows putative loci on all chromosomes except Y. There are >300 genes, markers and chromosomal regions that have been associated or linked with human obesity phenotypes. Our research group has used and contributed to the electronic version of the map that can be found at http://obesitygene.pbrc.edu.

As important as the genetics of obesity is, the impact that obesity has on the expression of deleterious genotypes

https://doi.org/10.1079/PNS2003313 Published online by Cambridge University Press

is of equal importance. It has been shown how BMI interacts with specific gene markers to augment the increased CHD risk associated with specific genotypes. Other loci, such as SR-BI (also known as SCARB1), the gene coding for the putative HDL receptor, in addition to the expected associations between specific alleles and lipid levels, show significant associations ($P < 0{\cdot}05$) between some of its variants and BMI (Acton *et al*. 1999). More recently, Elosua *et al*. (2003) have also shown clear evidence for interaction between BMI, the *APOE* gene and insulin resistance, giving support to the importance of researching and piecing together different components of the metabolic syndrome.

Bringing all together: nutrigenomics and nutrigenetics

Nutrigenomics and nutrigenetics are emerging and promising multidisciplinary systems that focus on studying the interactions between nutrition, genetics and health outcomes, using new technical and conceptual developments derived in part from the human genome project. Similar to the practice in the related fields of pharmacogenomics and pharmacogenetics (Lindpaintner, 2002), the terms nutrigenomics and nutrigenetics are largely used interchangeably. However, there are important conceptual differences in their approaches and aims (Peregrin, 2001; van Ommen & Stierum, 2002; Muller & Kersten, 2003; Trayhurn, 2003).

Nutrigenomics applies to the comprehensive genome-wide assessment of the effects of dietary factors or interventions. Nutrigenomics is concerned with the systematic assessment of how nutrients modify the overall expression pattern in cells and tissues of interest. In contrast to nutrigenetics, nutrigenomics does not focus on inter-individual differences in relation to the effects of nutrients, but rather focuses on differences among several dietary conditions or factors on quantitative measures of expression and their association with specific phenotypes.

Nutrigenetics, on the other hand, describes the interactions between nutrients (or dietary habits) and the characteristics of individuals, which to a certain extent will be determined by their genetic makeup. Thus, nutrigenetics is based on observations of dietary response in individuals and tests the hypothesis that interindividual differences in the observed response may be associated with the presence or absence of individual-specific biological markers, most commonly genetic polymorphisms, which may allow prediction of individual diet response.

Thus, although both nutrigenetics and nutrigenomics refer to the evaluation of nutrient effects using molecular biology technologies, the directionalities of their approaches are different. Nutrigenetics embodies the study of differences among individuals in relation to the response to a particular nutrient or dietary pattern, whereas nutrigenomics represents the study of differences among nutrients in relation to gene expression response in a single genome. Hence, the goals are distinct. Nutrigenetics will help in the clinical or public health settings to find the best dietary advice for the individual. Nutrigenomics will thrive in the setting of nutritional research to find the best 'diet' recommendation from a given series of nutritional alternatives.

The area of nutrigenetics is moving forward using the 'candidate gene' approach. Our own studies, and those of many other researchers, have focused on CVD genetics and interactions with dietary factors using large well-characterized population studies as well as dietary intervention trials (Ordovas, 2002, 2003; Ordovas *et al*. 2002*a*,*b*; Vincent *et al*. 2002; Masson *et al*. 2003; Perez-Martinez *et al*. 2003; Tai *et al*. 2003). These studies should help to put to rest the heated debate about the suitability of the traditional approach of recommending low-fat low-cholesterol diets for the entire population *v*. other recommendations based on the fact that some populations with relatively high intakes of non-saturated fats have very low rates of CVD and other chronic disorders (Hu, 2003).

Individuals that may respond better to one type of recommendation than another can now begin to be characterized under the controlled conditions of scientific research. Thus, a low-fat low-cholesterol strategy may be particularly beneficial in terms of lowering plasma cholesterol levels in those subjects carrying the apoE4 allele at the *APOE* gene (Ordovas, 2002). This strategy also applies to other CVD risk factors, such as HDL concentrations. The levels of HDL are also modulated by dietary, behavioural and genetic factors. It has been reported recently (Ordovas *et al*. 2002*a*) that the effect of dietary intake of PUFA on HDL-C concentrations is modulated by a common genetic polymorphism in the promoter region of the *APOA1* gene (Fig. 1). Thus, subjects carrying the A allele at the –75 G/A polymorphism show an increase in HDL-C concentrations with increased intakes of PUFA, whereas those homozygotes for the more common G allele have the expected lowering of HDL-C levels as the intake of PUFA increases. Thus, it could be predicted that subjects with low levels of HDL-C and

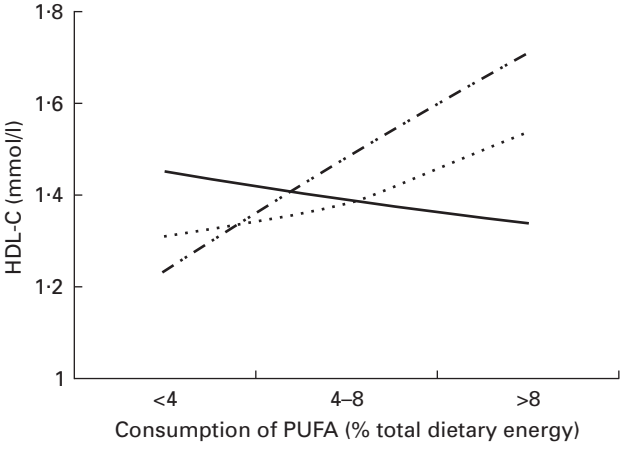

Fig. 1. PUFA modulate the effects of the *APOA1* –75(G/A) polymorphism on HDL-cholesterol (HDL-C) levels in the Framingham Study. Genotypes: (—), G/G; (· · · ·), G/A; (– ·· –), A/A. The GG genotype shows the expected decrease in serum HDL-C levels with increasing consumption of PUFA. Conversely, the presence of the A allele is associated with increasing concentrations of HDL-C. (Data from Ordovas *et al*. 2002*a*.)

https://doi.org/10.1079/PNS2003313 Published online by Cambridge University Press

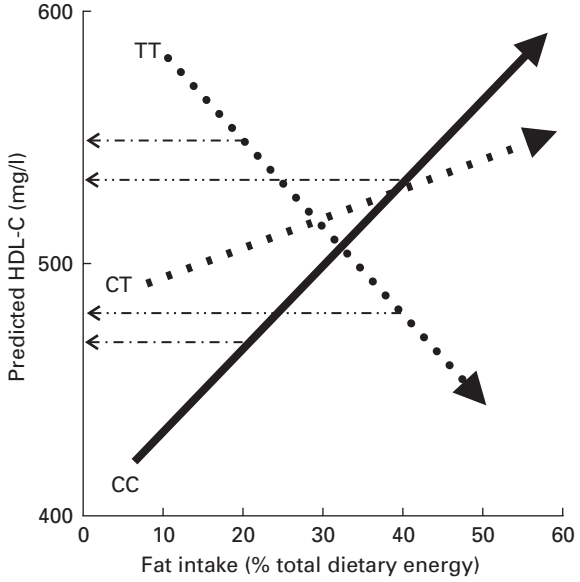

Fig. 2. The – 514 LIPC genotype (relating to the gene coding for hepatic lipase), dietary fat and HDL-cholesterol (HDL-C) levels in the Framingham Study. Subjects who are carriers of the CC genotype (▬▶) experience an increase in HDL-C with increased intakes of fat intake. Conversely, for those carrying the TT genotype (●●●▶) the trend is downwards. (▪▪▪▶), CT genotype. Two different scenarios are presented showing the hypothetical associations expected from studies carried out on populations consuming a very-low-fat diet (◀··–··, approximately 20% total dietary energy) or a high-fat diet (◀··–, approximately 40% total dietary energy). In one case (low fat consumption) the TT genotype will appear to be protective (higher HDL-C), whereas in the other scenario (high fat consumption), the TT genotype will be associated with lower HDL-C concentrations. (Data from Ordovas *et al.* 2002*b*.)

carriers of the A allele at the *APOA1* –75 G/A polymorphism may benefit from diets containing higher percentages of PUFA. However, it is important to emphasize that it is not yet the appropriate time to use this information in clinical practice, and even when the time comes, the recommendations will not be based on one single gene and they will have to be put in the context of global nutrition and health. In this specific example an increase in PUFA should be relative, and it would be necessary to replace other dietary components to avoid an increase in the energy intake. Similarly, the intake of antioxidants will have to be adjusted accordingly in order to account for the potential increase in oxidation of PUFA.

Our research group has recently reported another very interesting example of gene–diet interactions, i.e. between intake of fat, specifically of animal origin, and variability at the hepatic lipase gene, encoding a key enzyme involved in reverse cholesterol transport (Fig. 2; Ordovas *et al.* 2002*b*). Our data shows that subjects carrying the CC genotype (the most common among Caucasian subjects) 'react' to higher contents of fat in their diets by increasing the concentrations of HDL-C, which could be interpreted as a 'defence mechanism' to maintain the homeostasis of lipoprotein metabolism. Conversely, carriers of the TT genotype are not able to 'compensate' and, in fact, experience decreases in HDL-C levels. These data could identify a segment of the population particularly susceptible to diet-induced atherosclerosis. Moreover, considering the higher frequency of the T allele among certain ethnic groups (i.e. non-Caucasians), these data could shed some light on the impaired ability of certain ethnic groups to adapt to new nutritional environments, as clearly seen for Native Americans and Asian Indians (Tai *et al.* 2003). Finally, the data provides some clues concerning the reasons why genotype–phenotype association studies fail to show consistent results. In theory, this polymorphism at the hepatic lipase gene will show dramatically different outcomes in association studies depending on the dietary environment of the population studies, as shown in Fig. 2.

This knowledge should pave the way for successful dietary recommendations based on genetic factors that may help to reduce CVD risk more efficiently than the current universal recommendations. The same concept is clearly applicable to other age-related disorders. However, it should be realized that this stage is just the beginning of an interesting and revealing trip (Ordovas, 2003). The current knowledge is just a 'proof of concept', demonstrating that this approach should take us to our goal of preventing CVD or achieving safer and more efficacious therapies. It is important to keep in mind that there is no such thing as a 'silver bullet' for such complex and multifactorial traits as CVD. The examples presented here and those reported elsewhere (Masson *et al.* 2003; Ordovas, 2002; Vincent *et al.* 2002) represent just the very tip of the iceberg of the information that needs to be gathered in order to make safe and effective recommendations based on genetics, and that other approaches will be needed and can be incorporated within the concept of systems biology (van Ommen & Stierum, 2002; German *et al.* 2003).

Acknowledgements

Research supported by NIH/NHLBI grant no. HL54776, contracts 53-K06-5-10 and 58-1950-9-001 from the US Department of Agriculture Research Service.

References

Abate N & Chandalia M (2003) The impact of ethnicity on type 2 diabetes. *Journal of Diabetes Complications* **17**, 39–58.

Acton S, Osgood D, Donoghue M, Corella D, Pocovi M, Cenarro A, Mozas P, Keilty J, Squazzo S, Woolf EA & Ordovas JM (1999) Association of polymorphisms at the SR-BI gene locus with plasma lipid levels and body mass index in a white population. *Arteriosclerosis, Thrombosis and Vascular Biology* **19**, 1734–1743.

Baroukh N, Ostos MA, Vergnes L, Recalde D, Staels B, Fruchart J, Ochoa A, Castro G & Zakin MM (2001) Expression of human apolipoprotein A-I/C-III/A-IV gene cluster in mice reduces atherogenesis in response to a high fat-high cholesterol diet. *FEBS Letters* **502**, 16–20.

Birmingham K (2000) New data show life is longer, better, but more expensive. *Nature Medicine* **6**, 722.

Brotman DJ & Girod JP (2002) The metabolic syndrome: a tug-of-war with no winner. *Cleveland Clinical Journal of Medicine* **69**, 990–994.

https://doi.org/10.1079/PNS2003313 Published online by Cambridge University Press

Chagnon YC, Rankinen T, Snyder EE, Weisnagel SJ, Pérusse L & Bouchard C (2003) The human obesity gene map: The 2002 update. *Obesity Research* **11**, 313–367.
Cox NJ (2002) Calpain 10 and genetics of type 2 diabetes. *Current Diabetes Reports* **2**, 186–190.
Dawber TR, Meadors GF & Moore FEJ (1951) Epidemiological approaches to heart disease: the Framingham Study. *American Journal of Public Health* **41**, 279–286.
Deckelbaum RJ, Fisher EA, Winston M, Kumanyika S, Lauer RM, Pi-Sunyer FX, St Jeor S, Schaefer EJ & Weinstein IB (1999) Summary of a scientific conference on preventive nutrition: pediatrics to geriatrics. *Circulation* **100**, 450–456.
Elosua R, Demissie S, Cupples LA, Meigs JB, Wilson PWF, Schaefer EJ, Corella D & Ordovas JM (2003) Obesity modulates the association between apolipoprotein E genotype and fasting insulinemia and glucose in men. The Framingham Offspring Study. *Obesity Research* **11**, 1502–1508.
German JB, Roberts MA & Watkins SM (2003) Genomics and metabolomics as markers for the interaction of diet and health: lessons from lipids. *Journal of Nutrition* **133**, 2078S–2083S.
Gloyn AL (2003) The search for type 2 diabetes genes. *Ageing Research Reviews* **2**, 111–127.
Hanson RL & Knowler WC (2003) Quantitative trait linkage studies of diabetes-related traits. *Current Diabetes Reports* **3**, 176–183.
Hernan WH, Brandle M, Zhang P, Williamson DF, Matulik MJ, Ratner RE, Lachin JM & Engelgau MM (2003) Costs associated with the primary prevention of type 2 diabetes mellitus in the diabetes prevention program. *Diabetes Care* **26**, 36–47.
Hu FB (2003) The Mediterranean diet and mortality – olive oil and beyond. *New England Journal of Medicine* **348**, 2595–2596.
Kirkwood TB (2002) Evolution of ageing. *Mechanisms of Ageing and Development* **123**, 737–745.
Lindpaintner K (2002) The impact of pharmacogenetics and pharmacogenomics on drug discovery. *Nature Reviews Drug Discovery* **1**, 463–469.
McCarthy MI (2003) Growing evidence for diabetes susceptibility genes from genome scan data. *Current Diabetes Reports* **3**, 159–167.
McCrae T (1912) *Osler's Principles and Practice of Medicine*, p. 836. London: Appleton.
Mahaney MC, Blangero J, Rainwater DL, Mott GE, Comuzzie AG, MacCluer JW & VandeBerg JL (1999) Pleiotropy and genotype by diet interaction in a baboon model for atherosclerosis: a multivariate quantitative genetic analysis of HDL subfractions in two dietary environments. *Arteriosclerosis, Thrombosis and Vascular Biology* **19**, 1134–1141.
Mandell BF (2002) Who is conducting the deadly quartet? *Cleveland Clinical Journal of Medicine* **69**, 927.
Masson LF, McNeill G & Avenell A (2003) Genetic variation and the lipid response to dietary intervention: a systematic review. *American Journal of Clinical Nutrition* **77**, 1098–1111.
Meigs JB (2003) Epidemiology of the insulin resistance syndrome. *Current Diabetes Reports* **3**, 73–79.
Mercado MM, McLenithan JC, Silver KD & Shuldiner AR (2002) Genetics of insulin resistance. *Current Diabetes Reports* **2**, 83–95.
Muller M & Kersten S (2003) Nutrigenomics: goals and strategies. *Nature Reviews Genetics* **4**, 315–322.
Nambi V, Hoogwerf RJ & Sprecher DL (2002) A truly deadly quartet: obesity, hypertension, hypertriglyceridemia, and hyperinsulinemia. *Cleveland Clinical Journal of Medicine* **69**, 985–989.
National Cholesterol Education Program Adult Treatment Panel III (2002) Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. *Circulation* **106**, 3143–3421.
Ordovas JM (2002) Gene-diet interaction and plasma lipid responses to dietary intervention. *Biochemical Society Transactions* **30**, 68–73.
Ordovas JM (2003) Cardiovascular disease genetics: a long and winding road. *Current Opinion in Lipidology* **14**, 47–54.
Ordovas JM, Corella D, Cupples LA, Demissie S, Kelleher A, Coltell O, Wilson PW, Schaefer EJ & Tucker K (2002*a*) Polyunsaturated fatty acids modulate the effects of the APOA1 G-A polymorphism on HDL-cholesterol concentrations in a sex-specific manner: the Framingham Study. *American Journal of Clinical Nutrition* **75**, 38–46.
Ordovas JM, Corella D, Demissie S, Cupples LA, Couture P, Coltell O, Wilson PW, Schaefer EJ & Tucker KL (2002*b*) Dietary fat intake determines the effect of a common polymorphism in the hepatic lipase gene promoter on high-density lipoprotein metabolism: evidence of a strong dose effect in this gene-nutrient interaction in the Framingham Study. *Circulation* **106**, 2315–2321.
Peregrin T (2001) The new frontier of nutrition science: nutrigenomics. *Journal of the American Dietetic Association* **101**, 1306.
Perez-Martinez P, Ordovas JM, Lopez-Miranda J, Gomez P, Marin C, Moreno J, Fuentes F, Fernandez de la Puebla RA & Perez-Jimenez F (2003) 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. *American Journal of Clinical Nutrition* **77**, 809–813.
Quinn L (2003) Behavior and biology: the prevention of type 2 diabetes. *Journal of Cardiovascular Nursing* **18**, 62–68.
Rainwater DL, Kammerer CM, Carey KD, Dyke B, VandeBerg JF, Shelledy WR, Moore PH Jr, Mahaney MC, McGill HC Jr & VandeBerg JL (2002*a*) Genetic determination of HDL variation and response to diet in baboons. *Atherosclerosis* **161**, 335–343.
Rainwater DL, Kammerer CM, Cox LA, Rogers J, Carey KD, Dyke B, Mahaney MC, McGill HC Jr & VandeBerg JL (2002*b*) A major gene influences variation in large HDL particles and their response to diet in baboons. *Atherosclerosis* **163**, 241–248.
Rainwater DL, Kammerer CM & VandeBerg JL (1999) Evidence that multiple genes influence baseline concentrations and diet response of Lp(a) in baboons. *Arteriosclerosis, Thrombosis and Vascular Biology* **19**, 2696–2700.
Ravussin E & Bogardus C (2000) Energy balance and weight regulation: genetics versus environment. *British Journal of Nutrition* **83**, Suppl. 1, S17–S20.
Tai ES, Ordovas JM, Corella D, Deurenberg-Yap M, Chan E, Adiconis X, Chew SK, Loh LM & Tan CE (2003) The TaqIB and $-629C>A$ polymorphisms at the cholesteryl ester transfer protein locus: associations with lipid levels in a multiethnic population. The 1998 Singapore National Health Survey. *Clinical Genetics* **63**, 19–30.
The Diabetes Prevention Program Research Group (2000) The Diabetes Prevention Program: baseline characteristics of the randomized cohort. *Diabetes Care* **23**, 19–29.
Tinker A (2002) The social implications of an ageing population. *Mechanisms of Ageing and Development* **123**, 729–735.
Trayhurn P (2003) Nutritional genomics – 'Nutrigenomics'. *British Journal of Nutrition* **89**, 1–2.
Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V & Uusitupa M (2001)

https://doi.org/10.1079/PNS2003313 Published online by Cambridge University Press

Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *New England Journal of Medicine* **344**, 1343–1350.

US Department of Health and Human Services (2001) *The Surgeon General's Call to Action to Prevent and Decrease Overweight and Obesity*. Rockville, MD: US Department of Health and Human Services, Public Health Service, Office of the Surgeon General.

van Ommen B & Stierum R (2002) Nutrigenomics: exploiting systems biology in the nutrition and health arena. *Current Opinion in Biotechnology* **13**, 517–521.

Vincent S, Planells R, Defoort C, Bernard MC, Gerber M, Prudhomme J, Vague P & Lairon D (2002) Genetic polymorphisms and lipoprotein responses to diets. *Proceedings of the Nutrition Society* **61**, 427–434.

Wareham NJ, Franks PW & Harding AH (2002) Establishing the role of gene-environment interactions in the etiology of type 2 diabetes. *Endocrinology and Metabolism Clinics of North America* **31**, 553–566.

Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H & Kannel WB (1998) Prediction of coronary heart disease using risk factor categories. *Circulation* **97**, 1837–1847.

World Health Organization (2000) *World Health Report 2000. Health Systems: Improving Performance*. Geneva: WHO.

World Health Organization (2002) *World Health Report 2002. Reducing Risks, Promoting Healthy Life*. Geneva: WHO.

https://doi.org/10.1079/PNS2003313 Published online by Cambridge University Press