Proceedings of the Nutrition Society (2008), **67**, 206–213 doi:10.1017/S0029665108007040

The Summer Meeting of the Nutrition Society, hosted by the Irish Section, was held at the University of Ulster, Coleraine on 16–19 July 2007

Symposium on 'Diet and CVD'

Nutrigenetics and CVD: what does the future hold?

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CVD is a common killer in both the Western world and the developing world. It is a multifactorial disease that is influenced by many environmental and genetic factors. Although public health advice to date has been principally in the form of prescribed population-based recommendations, this approach has been surprisingly unsuccessful in reducing CVD risk. This outcome may be explained, in part, by the extreme variability in response to dietary manipulations between individuals and interactions between diet and an individual's genetic background, which are defined by the term 'nutrigenetics'. The shift towards personalised nutritional advice is a very attractive proposition. In principle an individual could be genotyped and given dietary advice specifically tailored to their genetic make-up. Evidence-based research into interactions between fixed genetic variants, nutrient intake and biomarkers of CVD risk is increasing, but still limited. The present paper will review the evidence for interactions between dietary fat and three common polymorphisms in the *apoE*, *apoAI* and *PPARγ* genes. Increased knowledge of how these and other genes influence dietary response should increase the understanding of personalised nutrition. While targeted dietary advice may have considerable potential for reducing CVD risk, the ethical issues associated with its routine use need careful consideration.

Nutrigenetics: ApoE, apoAI and PPARγ polymorphisms: CVD risk: Dietary fat

CVD is the leading cause of death worldwide, with mortality rates within the UK being amongst the highest in the world[1,2]. The existing knowledge of risk factors for CVD is extensive and supports well-established and accepted guidelines for the primary and secondary prevention of this disease. However, further understanding of the aetiology and efficacy of treatment and prevention of this complex multifactorial condition will require exploration of the interactions between genetic factors and the environment.

The fields of 'nutrigenomic' and 'nutrigenetic' research endeavour to provide a better understanding of the mechanisms of diet-related disease that ultimately will lead the way to a new approach of tailoring individual diets to enable optimal response according to individual genotypic variation, which will help to prevent, mitigate or cure chronic disease[3]. While the concepts of nutrigenomics and nutrigenetics are intimately linked, their meanings and purpose are fundamentally different in relation to understanding the relationship between diet and genes. Nutrigenomics considers the influence of specific nutrients or dietary constituents on gene expression and may facilitate prevention of diet-related common diseases, whereas nutrigenetics is concerned with the effects of fixed genetic variation, e.g. the effects of a single-nucleotide polymorphism (SNP) on responsiveness to diet[4]. Both these techniques have the potential to facilitate the prevention of chronic multifactorial diseases; nutrigenetics via an individualised approach to diet, nutrigenomics by a generic gene expression response to nutrients[5]. Despite these discrete definitions, the terms nutrigenomics and nutrigenetics are often used interchangeably and their specific distinction is lost. For the purpose of the present paper only the effect of genetic variation in relation to risk factors for CVD will be considered (nutrigenetics). To illustrate the complexity and confounding issues associated with nutrigenetics, and the interpretation of the study

Abbreviations: HDL-C, HDL-cholesterol; LDL-C, LDL-cholesterol; SNP, single-nucleotide polymorphism.

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outcomes, polymorphisms of three genes (*apoE*, *apoAI* and *PPARγ*) associated with CVD risk will be considered.

Disease management

Present methods of disease management are initiated by the diagnosis of disease at onset, which usually entails the identification of clinical symptoms or biochemical biomarkers such as raised plasma cholesterol. Treatments in the form of medicinal and nutritional therapy or lifestyle advice are often generalised, i.e. effectively 'one size fits all'. This approach has been relatively ineffective in disease management, in terms of public health recommendations failing to result in any appreciable benefit to the individual or because of a lack of compliance and motivation on the individual's behalf. However, with the advancement of nutrigenomic and nutrigenetic research a shift to a 'personalised nutrition' strategy seems attainable. A progression from treatment to early detection and prevention based on an individual's genetic predisposition seems achievable. Nutrigenetics and nutrigenomics may facilitate this unprecedented strategy for the management and prevention of CVD. However, there are important ethical issues associated with the use of personalised nutritional advice that require careful consideration.

Strategies for 'nutrigenetic' research

Although individuals share the same genome, there are many common variations in codon sequences amongst nutritionally-relevant genes. It is estimated that there are $>10 \times 10^6$ SNP that are present in >1% of the population[6]. Some common SNP that are therefore of public health relevance occur in 5–50% of the population. Most individuals are heterozygous for >50 000 SNP across their genes[7]. A number of these SNP result in alteration in proteins, the end product of gene expression, with altered structure or function. Understanding possible ways in which combinations of numerous SNP may influence metabolic responses to specific nutrients and nutrient requirements is potentially overwhelming, but as knowledge advances this information becomes more attainable and practical. There are several different approaches that can be employed to study diet–gene interactions: (1) a genome-wide linkage screen; (2) a candidate-gene approach.

Genome-wide linkage screen

A genome-wide linkage screen determines polymorphisms in the complete genome and relates these polymorphisms to a dependent variable. This process allows identification of genes that have a statistically significant relationship with the variable of interest. Although this method is often criticised for being non-hypothesis driven and can be described as a 'fishing exercise', it has identified unexpected and unpredictable genetic links that have advanced scientific knowledge substantially. An example is the recent report of a link between the non-functional *FTO* gene, the single-nucleotide polymorphism (SNP) rs993609, and the incidence of obesity[8]. It was reported that the A allele of this SNP is associated with an increased risk of being overweight or obese compared with the T allele (30% and 70% in carriers of one and two alleles respectively) in a white European population of adults and children (38 759 participants). The association is mediated through changes in fat mass and is observed from age 7 years onwards, with an interstitial deletion in the same region causing obesity[9].

Candidate-gene approach

The candidate-gene approach involves the selection and study of biologically-relevant genes. Genetic polymorphisms in these genes, known as SNP, can alter susceptibility to a disease. Likewise, dietary constituents may preferentially interact with a particular gene variant to influence disease risk. The identification of candidate or 'susceptible' genes should meet one or more of the following conditions:

1. genes that are chronically activated during a disease state and have been previously demonstrated to be sensitive to dietary intervention;
2. genes with functionally-important variations;
3. genes that have an important hierarchical role in biological cascades;
4. polymorphisms that are highly prevalent in the population (usually >10% for public health relevance);
5. genes with associated biomarkers, rendering clinical trials useful[10].

Rather than measuring all relevant SNP in a gene, it is of great benefit to identify haplotypes (haploid genotype). Haplotypes are a set of closely-linked genetic markers present on one chromosome, which tend to be inherited together (as they are not easily separated by recombination) with high linkage disequilibrium. Haplotypes can be identified by patterns of SNP with the use of HapMaps. Over the past few years, an international scientific consortium has characterised patterns of SNP linkage in haplotype blocks[7]. The identification of a few alleles in a haplotype block can unambiguously identify all other polymorphic sites in its region. Utilisation of these 'tag SNP' excludes the need to measure all SNP in the haplotype and facilitates practical SNP analysis for the nutrition scientist.

Nutrigenetic studies

There are an increasing number of published studies that have investigated the nutrigenetic links in relation to CVD risk and many dietary components. The following are examples of nutrient–gene interactions for which the evidence base is strongest.

Polymorphisms in apoE

The population response to changes in dietary fat intake has been extensively studied. A considerable extent of heterogeneity has been observed between individuals in

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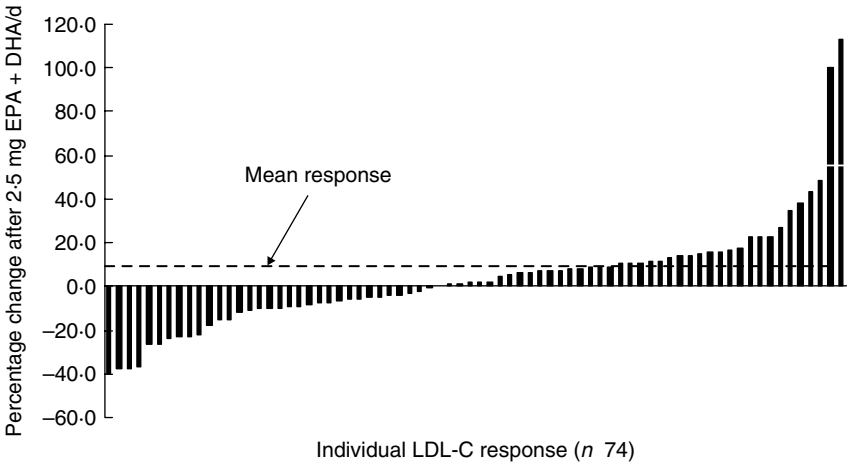

Fig. 1. LDL-cholesterol (LDL-C) response (% change) for seventy-four subjects following a 2·5 g EPA + DHA/d supplement for a 6-week period. (Data collated from Lovegrove *et al.*[15] and Brady *et al.*[16].)

response to the same dietary intervention. However, this variability is rarely addressed in any detail and is often ascribed to variable dietary compliance between participants. A classic example is the large variation that is observed in the concentration of serum LDL-cholesterol (LDL-C) in response to fish oil supplementation. The cardioprotective effects of the fatty acids in fish oil (EPA and DHA) are well recognised[11–13]. However, a potentially deleterious increase in LDL-C (5–10%) has been consistently reported after moderate to high doses of fish oil (>2 g EPA + DHA/d)[14–16]. Despite this small but significant increase in LDL-C, closer examination of the responses reveals a marked inter-individual variation. Fig. 1 illustrates the range of LDL-C responses for seventy-four subjects following a 2·5 mg EPA + DHA/d supplement for a 6-week period. There is a mean increase in LDL-C of 4·1%, yet the spread of individual responses is substantial, with values ranging from –40% to +113%. Thirty-three of the seventy-four subjects demonstrate a lower serum LDL-C and the remaining forty-one demonstrate higher LDL-C values following fish oil intervention (unpublished results collated from Lovegrove *et al.*[15] and Brady *et al.*[16]). This heterogeneous response to changes in dietary fat may be attributed to a number of factors including age, gender, baseline LDL-C levels, disease status and drug use. However, recent evidence strongly suggests that variation in a number of key genes may also be important, including common variants of the *apoE* gene.

The most convincing evidence to date for genotypic effects on dietary response comes from the extensively-studied *apoE* gene variant. The apoE protein has a central role in lipoprotein metabolism, being involved in chylomicron metabolism, VLDL synthesis and secretion and the cellular removal of lipoprotein remnants from the circulation[17–19]. This gene locus is polymorphic, with the identity of eighty-four gene variants being characterised to date. The best-known polymorphism is the common and widely-characterised apoE ε missense mutation, which results in three allelic isoforms, i.e. ε2, ε3 and ε4. The proteins produced from the different isoforms differ in the amino acid present at residue 112 (rs429358) and 158 (rs7412), with apoE2 containing Cys at both sites, apoE3 containing Cys at residue 112 and Arg at residue 158 and apoE4 containing Arg at both positions[20,21]. The prevalence of this SNP varies in different populations. It has been reported that approximately 65% of Caucasians are homozygous E3/E3, 21% are E4 carriers (E3/E4 or E4/E4), 11% are E2 carriers (E2/E2 or E2/E3) and the remaining 4% have an E2/E4 genotype[22,23].

The impact of the apoE genotype on CVD risk has been extensively investigated over the past 30 years. A meta-analysis has been published recently that summarises the overall findings from studies using a variety of end-point measures[24]. A mean 40–50% increase in CHD risk was observed in E4 carriers (overall OR 1·42) relative to the wild-type E3/E3 genotype, with no apparent differences for either the E2 and E3 subgroups (OR 0·98). Although a causal mechanism to link E4 with increased CHD risk has not been fully elucidated, the association has been ascribed to a higher concentration of LDL-C. This higher LDL-C is believed to arise from the apoE4 isoform having a relatively higher affinity for its membrane (LDL/chylomicron remnant) receptor and feedback inhibition of receptor activity in E4 carriers[22]. Other mechanisms relating to reduced antioxidant status may also be operative[25].

Numerous studies have shown significant interactions between the three apoE isoforms in relation to responsiveness to dietary total fat content and fatty acid composition, total cholesterol, fish oil consumption and alcohol intake[14,26–36]. A systematic review has identified forty-six studies that have examined the apoE locus and alterations in dietary fat content[37]. Significantly different responses in total cholesterol and LDL-C by apoE genotype were reported in eight and eleven studies respectively, with the apoE4 individuals generally being the most responsive. It has been suggested that variability in response to a high-carbohydrate diet may also be determined by this genotype, although the response to a high-MUFA diet was found to be linked to waist circumference[38]. ApoE genotype-dependent effects of diets rich in either

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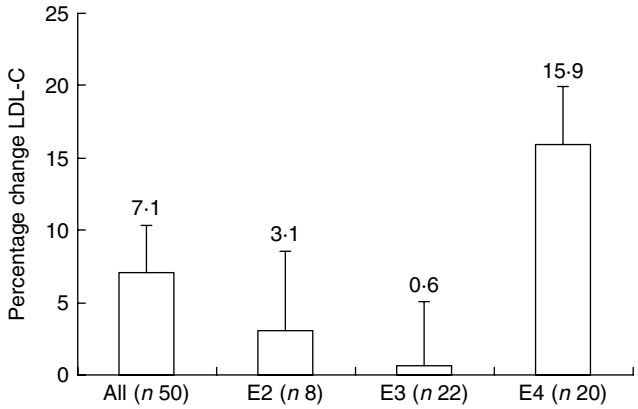

Fig. 2. Impact of apoE genotype on LDL response to 3 g EPA + DHA/d. (Adapted from Minihane *et al.*[14].)

carbohydrate or MUFA have also been noted[39]. Inconsistency in nutrient–gene interactions in relation to apoE polymorphisms may be a result, in part, of retrospective genotyping of small study cohorts, for which the genotype–diet–LDL-C interactions were not the primary outcome. This factor has resulted in the under-representation of the less-frequent genotypes and, although trends may have been evident, many of the studies were clearly under-powered to detect significant genotype–treatment effects. The prospective genotyping of larger study cohorts has been used as an alternative approach to increase statistical power.

To date only one study has examined the apoE genotype–dietary fat–LDL-C association using prospective recruitment by genotype. A significant effect of apoE genotype on the plasma lipid response to a low-fat diet was reported, with a 5%, 13% and 16% reduction in LDL-C in E3/E3, E3/E4 and E4/E4 males respectively[26]. Other studies have examined the association between apoE genotype and fish oil (EPA and DHA) on LDL-C responses. In a retrospectively genotyped study the mean 7·1% increase in LDL-C for the group as a whole was observed to be entirely attributable to a 16% rise in LDL-C in the apoE4 participants, and it was speculated that apoE genotype may, in part, predict the blood lipid response to fish oil intervention (Fig. 2)[14]. Two prospectively-genotyped studies designed to test the hypothesis that apoE polymorphism has a significant effect on the LDL-C response to EPA and DHA have recently been completed. Data from these studies demonstrate that (a) apoE–fish oil–LDL-C interactions are only evident at intakes >2 g EPA + DHA/d (AM Minihane, personal communication); (b) it is the DHA rather than the EPA in fish oils that is responsible for the LDL-C raising effects in E4 individuals (AM Minihane, personal communication). These studies provide examples of the potential of prospective genotyping in nutrigenetic research.

ApoAI polymorphisms

Another example of a well-documented nutrigenetic interaction for which there is a strong evidence base is that of *apoAI* gene, which is a major structural and functional

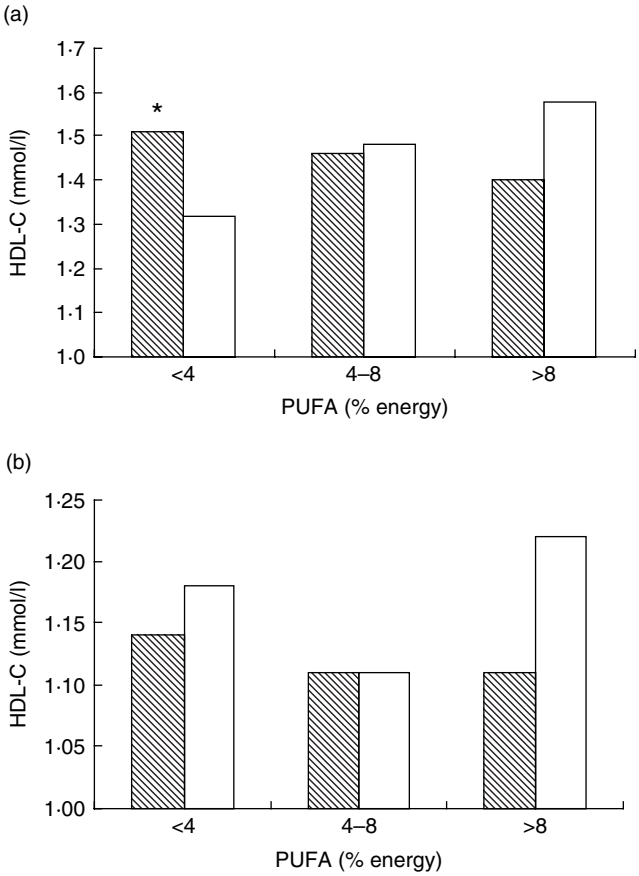

Fig. 3. Impact of apoAI genotype (G/G (\\\), and GA + AA (□)) on HDL-cholesterol (HDL-C; mmol/l) influenced by habitual PUFA intake and gender ((a) women and (b) men). Mean value for G/G carriers was significantly different from that for A allele carriers: $*P = 0{\cdot}015$). ApoAI genotype frequency GG 70%, GA 26% and AA 4%. (Adapted from Ordovas *et al.*[42].)

component of HDL[40]. HDL-cholesterol (HDL-C) is a protective factor for CVD that is independently and inversely linked to CVD risk[41]. The *apoAI* gene is highly polymorphic and the –75G/A SNP, a common variant of this gene, has been extensively studied in relation to variation in the concentration of serum apoAI and HDL-C. However, the reported associations between plasma apoAI concentrations and circulating HDL-C levels have been conflicting, and from recent evidence it seems probable that the inconsistencies between studies are a result of contributions from background diet and gender[40]. A significant interaction between this polymorphism and PUFA intake in determining plasma HDL-C concentration has been demonstrated in women in the Framingham Study[42]. In carriers of the A allele higher PUFA intakes (>8% energy) were shown to be associated with higher HDL-C, whereas in G/G homozygotes, the opposite effect was observed. At low PUFA intakes (<4% energy) G/G females were found to have approximately 14% higher HDL-C concentrations than A allele carriers. At high PUFA intakes (>8% energy) females carrying the A allele were found to have 13% higher HDL-C levels than G/G females[42] (Fig. 3). However, in the 755 men studied

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PUFA intake was found to have no significant effect on HDL-C concentration. This outcome is an example of how the background diet and gender can significantly affect the association between a particular genotype and a biological risk marker. Conflicting results will therefore result if populations consuming different habitual diets are studied. These inconsistencies in reported study outcomes are not necessarily a result of inherent differences, but are a result of a nutrient–gene interaction, i.e. a classic example of where individualised dietary advice could be important in relation to exerting a positive influence on HDL-C levels and CVD risk[40].

PPARγ

PPARγ is a nuclear transcription factor involved in the regulation of a number of key genes in relation to fat metabolism and inflammation[43,44]. It is expressed predominantly, although not exclusively, in adipose tissue in which it regulates adipocyte differentiation and fat metabolism through a complex programme of gene expression[45]. PPARγ is also present in other tissues such as muscle, monocytes and the endothelium in which it also plays a role in controlling insulin sensitivity, blood pressure and inflammation[46]. As a consequence of these regulatory functions PPARγ is involved in the development of obesity and is a prime candidate gene for CVD nutrigenetic research[45]. A common polymorphism of the *PPARγ* gene (pro12ala) has been widely studied and may be associated with an increased risk of adiposity and insulin resistance[47], but a decreased risk of metabolic syndrome and type 2 diabetes[48–50]. A more efficient suppression of lipolysis and lower circulating NEFA concentrations have been observed in pro12ala carriers during a hyperinsulinaemic-euglycaemic clamp[51]. However, in another study no relationship between fasting NEFA levels and the polymorphism was found in the general population[52].

Despite extensive research into the interactions between pro12ala and dietary fat intake, the reported outcomes are somewhat conflicting. In one study total dietary fat intake was found to have no effect on the BMI of individuals with the pro12ala polymorphism compared with wild-type (pro12pro) individuals[53]. Carriers of the pro12ala variant were reported to have a higher BMI than non-carriers within the lowest quintile of total fat intake. Total fat intake was shown to be directly correlated with plasma HDL-C among pro12ala variant carriers; in contrast, among pro12pro homozygotes total fat intake was inversely correlated with HDL-C and total cholesterol. Intake of SFA was found to be associated with increased BMI in both genotypes, whereas there was no association between MUFA intake and BMI in pro12pro individuals, but an inverse association in the 12ala polymorphism carriers. In a study of the effect of diet and the *PPARγ* gene on components of the metabolic syndrome total dietary fat intake was reported to be correlated positively with BMI only among homozygous wild-type pro12pro individuals[54]. Similar results were obtained when saturated fat intake was considered. Total fat and saturated fat intakes were also found to be positively correlated with fasting glucose, waist circumference and total cholesterol:HDL-C and negatively correlated with HDL-C only in pro12pro carriers. These two studies failed to confirm the interaction between dietary PUFA:SFA and this polymorphism that was observed in a study that reported an inverse relationship between dietary PUFA:SFA and both BMI and fasting insulin in ala12 carriers, but not in pro12 homozygotes[55]. Nevertheless, when the analysis was repeated for total fat intake no interaction between genotype and BMI or fasting insulin was found. However, evidence has been provided to support the existence of an interaction between this polymorphism and obesity according to diet[50]. Obese subjects with the ala12 allele who consumed fewer MUFA were found to be more insulin resistant. However, this study was undertaken in a Mediterranean population with a high intake of MUFA, whereas the previously mentioned studies were conducted in populations with diets rich in PUFA. In a 3-year longitudinal study in which subjects with impaired glucose tolerance were randomised to an exercise and low-fat-diet group *v.* a control group, ala/ala homozygotes were reported to have lost more weight than pro/pro and pro/ala subjects in the intervention arm[56]. In another study pro12ala individuals were found to have lost similar amounts of weight to pro/pro subjects following hypoenergetic diets, although they had more carbohydrate oxidation, less fat oxidation and a greater response in insulin sensitivity[57]. However, no significant interaction between pro12ala and BMI, glucose or fat tolerance or fasting levels of glucose, lipids or insulin was found in young healthy subjects[58]. This finding suggests that the differential effect that this polymorphism has on weight and related metabolic disorders may only become apparent later in life. In a fish oil supplementation study carriers of the ala12 allele were reported to have presented with a greater decrease in plasma TAG after *n*-3 PUFA supplementation when total fat intake was <37% energy or the intake of SFA was <10% energy[59]. No evidence of a differential effect of *n*-3 PUFA supplementation by genotype on fasting insulin or glucose was found.

These studies suggest that the PPARγ pro12ala polymorphism can modulate the association between dietary fat intake and cardiovascular risk factors, but the association is not simple, with differential nutrient–gene–environment–gender interactions being multifaceted and extremely difficult to interpret. The complex interactions that occur in the SNP of one gene highlights the requirement for very careful data analysis and the need to pool all datasets available from individual groups in order to gain a more complete picture of nutrigenetics in relation to this SNP. Nevertheless, PPARγ and its agonists are currently under intense investigation as potential therapeutic targets for obesity and insulin resistance[60].

Challenges in nutrigenetic research

Nutrigenetics is in its infancy and standardised protocols are not yet established. A comparison of studies is challenging and conclusions often difficult to draw. As discussed previously, studies have often been of retrospective design and thus have been of insufficient power to

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detect nutrient–gene associations. Prospective genotyping increases the power to resolve these associations and should be used whenever possible. With any research publication bias results in positive associations being reported more often than negative associations, which may provide a false impression of the level of significance of many nutrient–gene interactions.

Many studies published in the area of nutrigenetics have only considered one SNP in a single gene, with little consideration being given to multiple nutrient–gene–environment interactions[14,26,54,60]. Although this approach is scientifically valid and invaluable for determination of mechanistic disease aetiology, the development of specific personalised nutritional advice requires the determination of multiple gene–nutrient–environment–gender interactions. For this purpose the development of haplotype databases and biobanks are required, in which data can be collated, allowing a more complete understanding of potential nutrigenetic interactions. These databases and biobanks are expensive and difficult to establish, but a necessity if nutrigenetic research is to progress.

The advancement of techniques paramount for nutrigenetic research has been very rapid, yet these methods are still relatively new and under continuous development. From these techniques a large and complex dataset is generated that requires careful and perceptive interpretation. It is critical for the determination of useful individualised nutritional advice that nutrition scientists with specialist knowledge of interaction between nutrients and biological systems are involved in the development of data interpretation.

Ethical issues and personalised nutrition advice

For personalised nutrition to become a viable option there are numerous considerations and unavoidable assumptions that need to be considered before it can be widely applied. It is still unknown whether individuals will want to undertake genetic tests or in fact understand the concept of such technology. A survey of 1000 Americans conducted in 2003 has reported that 62% of respondents had never heard of 'nutrigenomics'[61]. However, if specific products did arise from nutrigenomic research those interviewed did express interest in an in-depth well-being assessment and also a strong interest in vitamins, fortified foods and natural foods. More research is required to determine whether individuals would want to undergo such tests and the value to that individual of knowledge of a specific personalised nutrition regimen. There is already a large gap between the existing dietary guidelines and what individuals actually eat[62]. Knowledge of being at higher than average risk of CVD may motivate individuals to actually make positive changes to their diets. However, genetic testing could undermine current healthy eating messages by implying that only those with the 'risky gene' need to eat a healthy diet. These questions are important, unanswered and must be addressed if personalised nutritional advice is to become part of mainstream disease prevention and treatment. It may be that genotype–phenotype–environment interactions are too complex to fully unravel and solve with practicable dietary interventions.

Moreover, it is important to consider whether the genetic tests and personalised food products will be affordable, cost-effective and socially acceptable. It is of concern that only those well informed and with sufficient funds would be able to take advantage of such technology and personal advice. Also, if genetic testing has been undertaken, would this information be available to a third party, such as insurance companies, who could use it to the detriment of the individual, potentially affecting the availability of insurance or increasing the premium cost?

There is some resistance to the use and perceived effectiveness of personalised nutrition based on genomics and whether this approach can be a solution to diseases caused by unhealthy foods[63]. It has been suggested that it may be more beneficial to use current risk factors as a basis for population screening and controlling CVD[64]. There has also been dialogue on the social, economic and environmental causes of CVD as well as the biological causes, shifting the emphasis away from an individual's diet to food manufacturing as being more effective in disease management[63].

The nutrigenetics field is still very much in its infancy, but the potential for targeting dietary recommendations to individuals based on genotype will increase as further links between polymorphisms and CVD risk factors are characterised. Although there is enormous potential in personalising dietary advice, the practical application of nutrigenetics in the management of diet-related disease is still some way off.

Conclusion

The development of publicly-available SNP and haplotype databases, with links to health outcomes, biomarker and environmental exposure data in the form of biobanks, promises a future revolution in preventative health care. However, while there is evidence for nutrient–gene interactions, there are inconsistencies between studies that will limit the application of nutrigenetics in diet-related disease in the immediate future. In addition to the need for adequately-powered intervention studies, greater attention should be given to other issues such as the acceptance by the public of genetic testing.

Acknowledgements

J.A.L. and R.G. prepared the manuscript. There is no conflict of interest.

References

1. Allender S, Peto V, Scarborough P, Boxer A & Rayner M (2007) *Coronary Heart Disease Statistics 2007*. London: British Heart Foundation.
2. British Heart Foundation (2003) Coronary heart disease statistics. http://dphpc.ox.ac.uk/bhfhprg/stats/2003/

3. Kaput J & Rodriguez RL (2004) Nutritional genomics: the next frontier in the postgenomic era. *Physiol Genomics* **16**, 166–177.
4. Ordovas JM & Mooser V (2004) Nutrigenomics and nutrigenetics. *Curr Opin Lipidol* **15**, 101–108.
5. Corthesy-Theulaz I, den Dunnen JT, Ferre P, Geurts JM, Muller M, van Belzen N & van Ommen B (2005) Nutrigenomics: the impact of biomics technology on nutrition research. *Ann Nutr Metab* **49**, 355–365.
6. McVean G, Spencer C & Chaix R (2005) Perspectives on human genetic variation from the HapMap project. *PLoS Genet* **1**, e54.
7. Hinds D, Stuve L, Nilsen GB, Halperin E, Eskin E, Ballinger D, Frazer KA & Cox DR (2005) Whole -genome patterns of common DNA variation in three human populations. *Science* **307**, 1052–1053.
8. Frayling TM, Timpson NJ, Weedon MN *et al.* (2007) A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. *Science* **316**, 889–894.
9. Stratakis CA, Lafferty A, Taymans SE, Gafni RI, Meck JM & Blancato J (2000) Anisomastia associated with interstitial duplication of chromosome 16, mental retardation, obesity, dysmorphic facies, and digital anomalies: molecular mapping of a new syndrome by fluorescent in situ hybridization and microsatellites to 16q13 (D16S419-D16S503). *J Clin Endocrinol Metab* **85**, 3396–3401.
10. Mutch DM, Wahli W & Williamson G (2005) Nutrigenomics and nutrigenetics: the emerging faces of nutrition. *FASEB J* **19**, 1602–1616.
11. Bucher HC, Hengstler P, Schindler C & Meier G (2002) N-3 polyunsaturated fatty acids in coronary heart disease: a meta-analysis of randomized controlled trials. *Am J Med* **112**, 298–304.
12. Burr L, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, Elwood PC & Deadman NM (1989) Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: Diet and reinfarction trial (DART). *Lancet* **ii**, 757–761.
13. Kris-Etherton P, Harris W & Appel L (2003) Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Arterioscler Thromb Vasc Biol* **23**, E31–E42.
14. Minihane AM, Khan S, Leigh-Firbank EC, Talmud P, Wright JW, Murphy MC, Griffin BA & Williams CM (2000) ApoE polymorphism and fish oil supplementation in subjects with an atherogenic lipoprotein phenotype. *Arterioscler Thromb Vasc Biol* **20**, 1990–1997.
15. Lovegrove JA, Lovegrove SS, Lesauvage SV, Brady LM, Saini N, Minihane AM & Williams CM (2004) Moderate fish-oil supplementation reverses low-platelet, long-chain n-3 polyunsaturated fatty acid status and reduces plasma triacylglycerol concentrations in British Indo-Asians. *Am J Clin Nutr* **79**, 974–982.
16. Brady LM, Lovegrove SS, Lesauvage SV, Gower BA, Minihane AM, Williams CM & Lovegrove JA (2004) Increased n-6 polyunsaturated fatty acids do not attenuate the effects of long-chain n-3 polyunsaturated fatty acids on insulin sensitivity or triacylglycerol reduction in Indian Asians. *Am J Clin Nutr* **79**, 983–991.
17. Huang Y, Ji ZS, Brecht WJ, Rall SC Jr, Taylor JM & Mahley RW (1999) Overexpression of apolipoprotein E3 in transgenic rabbits causes combined hyperlipidemia by stimulating hepatic VLDL production and impairing VLDL lipolysis. *Arterioscler Thromb Vasc Biol* **19**, 2952–2959.
18. Mahley RW (1988) Apolipoprotein E: cholesterol transport protein with expanding role in cell biology. *Science* **240**, 622–630.
19. Minihane AM, Jofre-Monseny L, Olano-Martin E & Rimbach GH (2007) Apolipoprotein E genotype, cardiovascular risk and responsiveness to dietary fat manipulation. *Proc Nutr Soc* **66**, 183–197.
20. Rall SC Jr, Weisgraber KH & Mahley RW (1982) Human apolipoprotein E (). The complete amino acid sequence. *J Biol Chem* **257**, 4171–4178.
21. Weisgraber KH (1990) Apolipoprotein E distribution among human plasma lipoproteins: role of the cysteine-arginine interchange at residue 112. *J Lipid Res* **31**, 1503–1511.
22. Eichner JE, Dunn ST, Perveen G, Thompson DM, Stewart KE & Stroehla BC (2002) Apolipoprotein E polymorphism and cardiovascular disease: a HuGE review. *Am J Epidemiol* **155**, 487–495.
23. Singh P, Singh M & Mastana S (2006) ApoE distribution in world populations with new data from India and the UK. *Ann Hum Biol* **33**, 297–308.
24. Song Y, Stampfer MJ & Liu S (2004) Meta-analysis: apolipoprotein E genotypes and risk for coronary heart disease. *Ann Intern Med* **141**, 137–147.
25. Minihane AM, Jofre-Monseny L, Olano-Martin E & Rimbach G (2007) ApoE genotype, cardiovascular risk and responsiveness to dietary fat manipulation. *Proc Nutr Soc* **66**, 183–197.
26. Sarkkinen E, Korhonen M, Erkkila A, Ebeling T & Uusitupa M (1998) Effect of apolipoprotein E polymorphism on serum lipid response to the separate modification of dietary fat and dietary cholesterol. *Am J Clin Nutr* **68**, 1215–1222.
27. Miettinen TA, Gylling H, Vanhanen H & Ollus A (1992) Cholesterol absorption, elimination, and synthesis related to LDL kinetics during varying fat intake in men with different apoprotein E phenotypes. *Arterioscler Thromb* **12**, 1044–1052.
28. Lehtimaki T, Moilanen T, Solakivi T, Laippala P & Ehnholm C (1992) Cholesterol-rich diet induced changes in plasma lipids in relation to apolipoprotein E phenotype in healthy students. *Ann Med* **24**, 61–66.
29. Friedlander Y, Berry EM, Eisenberg S, Stein Y & Leitersdorf E (1995) Plasma lipids and lipoproteins response to a dietary challenge: analysis of four candidate genes. *Clin Genet* **47**, 1–12.
30. Tso TK, Park S, Tsai YH, Williams G & Snook JT (1998) Effect of apolipoprotein E polymorphism on serum lipoprotein response to saturated fatty acids. *Lipids* **33**, 139–148.
31. Dreon DM, Fernstrom HA, Miller B & Krauss RM (1995) Apolipoprotein E isoform phenotype and LDL subclass response to a reduced-fat diet. *Arterioscler Thromb Vasc Biol* **15**, 105–111.
32. Schaefer EJ, Lamon-Fava S, Ausman LM, Ordovas JM, Clevidence BA, Judd JT, Goldin BR, Woods M, Gorbach S & Lichtenstein AH (1997) Individual variability in lipoprotein cholesterol response to National Cholesterol Education Program Step 2 diets. *Am J Clin Nutr* **65**, 823–830.
33. Lopez-Miranda J, Ordovas JM, Mata P, Lichtenstein AH, Clevidence B, Judd JT & Schaefer EJ (1994) Effect of apolipoprotein E phenotype on diet-induced lowering of plasma low density lipoprotein cholesterol. *J Lipid Res* **35**, 1965–1975.
34. Tikkanen MJ, Huttunen JK, Ehnholm C & Pietinen P (1990) Apolipoprotein E4 homozygosity predisposes to serum cholesterol elevation during high fat diet. *Arteriosclerosis* **10**, 285–288.
35. Manttari M, Koskinen P, Ehnholm C, Huttunen JK & Manninen V (1991) Apolipoprotein E polymorphism influences the serum cholesterol response to dietary intervention. *Metabolism* **40**, 217–221.

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36. Schaefer EJ, Lichtenstein AH, Lamon-Fava S, Contois JH, Li Z, Rasmussen H, McNamara JR & Ordovas JM (1995) Efficacy of a National Cholesterol Education Program Step 2 diet in normolipidemic and hypercholesterolemic middle-aged and elderly men and women. *Arterioscler Thromb Vasc Biol* **15**, 1079–1085.
37. Masson LF, McNeill G & Avenell A (2003) Genetic variation and the lipid response to dietary intervention: a systematic review. *Am J Clin Nutr* **77**, 1098–1111.
38. Couture P, Archer WR, Lamarche B, Landry N, Deriaz O, Corneau L, Bergeron J & Bergeron N (2003) Influences of apolipoprotein E polymorphism on the response of plasma lipids to the ad libitum consumption of a high-carbohydrate diet compared with a high-monounsaturated fatty acid diet. *Metabolism* **52**, 1454–1459.
39. Moreno JA, Perez-Jimenez F, Marin C, Gomez P, Perez-Martinez P, Moreno R, *et al.* (2004) The effect of dietary fat on LDL size is influenced by apolipoprotein E genotype in healthy subjects. *J Nutr* **134**, 2517–2522.
40. Ordovas JM (2006) Genetic interactions with diet influence the risk of cardiovascular disease. *Am J Clin Nutr* **83**, 443S–446S.
41. Wilson PW, Abbott RD & Castelli WP (1988) High density lipoprotein cholesterol and mortality. The Framingham Heart Study. *Arteriosclerosis* **8**, 737–741.
42. Ordovas JM, Corella D, Cupples LA, Demissie S, Kelleher A, Coltell O, Wilson PWF, Schaefer EJ & Tucker K (2002) Polyunsaturated fatty acids modulate the effects of the APOA1 G-A polymorphism on HDL-cholesterol concentrations in a sex-specific manner: the Framingham Study. *Am J Clin Nutr* **75**, 38–46.
43. Auwerx J (1999) PPARgamma, the ultimate thrifty gene. *Diabetologia* **42**, 1033–1049.
44. Rosen ED & Spiegelman BM (2001) PPARgamma: a nuclear regulator of metabolism, differentiation, and cell growth. *J Biol Chem* **276**, 37731–37734.
45. Cecil JE, Watt P, Palmer CN & Hetherington M (2006) Energy balance and food intake: the role of PPARgamma gene polymorphisms. *Physiol Behav* **88**, 227–233.
46. Memisoglu A, Hu FB, Hankinson SE, Liu S, Meigs JB, Altshuler DM, Hunter DJ & Manson JE (2003) Prospective study of the association between the proline to alanine codon 12 polymorphism in the PPARgamma gene and type 2 diabetes. *Diabetes Care* **26**, 2915–2917.
47. Gonzalez Sanchez JL, Serrano Rios M, Fernandez Perez C, Laakso M & Martinez Larrad MT (2002) Effect of the Pro12Ala polymorphism of the peroxisome proliferator-activated receptor gamma-2 gene on adiposity, insulin sensitivity and lipid profile in the Spanish population. *Eur J Endocrinol* **147**, 495–501.
48. Frederiksen L, Brodbaek K, Fenger M, Jorgensen T, Borch-Johnsen K, Madsbad S & Urhammer SA (2002) Studies of the Pro12Ala polymorphism of the PPAR-gamma gene in the Danish MONICA cohort: homozygosity of the Ala allele confers a decreased risk of the insulin resistance syndrome. *J Clin Endocrinol Metab* **87**, 3989–3992.
49. Altshuler D, Hirschhorn JN, Klannemark M *et al.* (2000) The common PPARgamma Pro12Ala polymorphism is associated with decreased risk of type 2 diabetes. *Nat Genet* **26**, 76–80.
50. Soriguer F, Morcillo S, Cardona F, Rojo-Martinez G, de la Cruz Almaraz M, de la Soledad Ruiz de Adana M, Olveira G, Tinahones F & Esteva I (2006) Pro12Ala polymorphism of the PPARG2 gene is associated with type 2 diabetes mellitus and peripheral insulin sensitivity in a population with a high intake of oleic acid. *J Nutr* **136**, 2325–2330.
51. Stumvoll M, Wahl HG, Loblein K, Becker R, Machicao F, Jacob S & Häring H (2001) Pro12Ala polymorphism in the peroxisome proliferator-activated receptor-gamma2 gene is associated with increased antilipolytic insulin sensitivity. *Diabetes* **50**, 876–881.
52. Vaccaro O, Mancini FP, Ruffa G *et al.* (2002) Fasting plasma free fatty acid concentrations and Pro12Ala polymorphism of the peroxisome proliferator-activated receptor (PPAR) gamma2 gene in healthy individuals. *Clin Endocrinol (Oxf)* **57**, 481–486.
53. Memisoglu A, Hu FB, Hankinson SE, Manson JE, De Vivo I, Willett WC & Hunter DJ (2003) Interaction between a peroxisome proliferator-activated receptor gamma gene polymorphism and dietary fat intake in relation to body mass. *Hum Mol Genet* **12**, 2923–2929.
54. Robitaille J, Despres JP, Perusse L & Vohl MC (2003) The PPAR-gamma P12A polymorphism modulates the relationship between dietary fat intake and components of the metabolic syndrome: results from the Quebec Family Study. *Clin Genet* **63**, 109–116.
55. Luan J, Browne PO, Harding AH, Halsall DJ, O'Rahilly S, Chatterjee VK & Wareham NJ (2001) Evidence for gene-nutrient interaction at the PPARgamma locus. *Diabetes* **50**, 686–689.
56. Lindi VI, Uusitupa MI, Lindstrom J *et al.* (2002) Association of the Pro12Ala polymorphism in the PPAR-gamma2 gene with 3-year incidence of type 2 diabetes and body weight change in the Finnish Diabetes Prevention Study. *Diabetes* **51**, 2581–2586.
57. Nicklas BJ, van Rossum EF, Berman DM, Ryan AS, Dennis KE & Shuldiner AR (2001) Genetic variation in the peroxisome proliferator-activated receptor-gamma2 gene (Pro12Ala) affects metabolic responses to weight loss and subsequent weight regain. *Diabetes* **50**, 2172–2176.
58. Poirier O, Nicaud V, Cambien F & Tiret L (2000) The Pro12Ala polymorphism in the peroxisome proliferator-activated receptor gamma2 gene is not associated with post-prandial responses to glucose or fat tolerance tests in young healthy subjects: the European Atherosclerosis Research Study II. *J Mol Med* **78**, 346–351.
59. Lindi V, Schwab U, Louheranta A *et al.* (2003) Impact of the Pro12Ala polymorphism of the PPAR-gamma2 gene on serum triacylglycerol response to n-3 fatty acid supplementation. *Mol Genet Metab* **79**, 52–60.
60. Olefsky JM & Saltiel AR (2000) PPAR gamma and the treatment of insulin resistance. *Trends Endocrinol Metab* **11**, 362–368.
61. Cogent (2003) Congent syndicated genomics attitudes and trends: consumers. http://www.cogentresearch.com/products/CGAT%20Brochurepdf
62. Henderson L, Gregory J & Swan G (2003) *The National Diet and Nutrition Survey: Adults Aged 19–64 Years*. London: The Stationery Office.
63. Cannon G & Leitzmann C (2005) The new nutrition *Science* project. *Public Health Nutr* **8**, 673–694.
64. McCluskey S, Baker D, Percy D, Lewis P & Middleton E (2007) Reductions in cardiovascular risk in association with population screening: a 10-year longitudinal study. *J Public Health (Oxf)* **29**, 379–387.

https://doi.org/10.1017/S0029665108007040 Published online by Cambridge University Press