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Nutrition Society Silver Medal Lecture
Nutrigenetics and personalised nutrition: how far have we progressed and are we likely to get there?

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Nutrigenetics and personalised nutrition are components of the concept that in the future genotyping will be used as a means of defining dietary recommendations to suit the individual. Over the last two decades there has been an explosion of research in this area, with often conflicting findings reported in the literature. Reviews of the literature in the area of apoE genotype and cardiovascular health, apoA5 genotype and postprandial lipaemia and perilipin and adiposity are used to demonstrate the complexities of genotype–phenotype associations and the aetiology of apparent between-study inconsistencies in the significance and size of effects. Furthermore, genetic research currently often takes a very reductionist approach, examining the interactions between individual genotypes and individual disease biomarkers and how they are modified by isolated dietary components or foods. Each individual possesses potentially hundreds of 'at-risk' gene variants and consumes a highly-complex diet. In order for nutrigenetics to become a useful public health tool, there is a great need to use mathematical and bioinformatic tools to develop strategies to examine the combined impact of multiple gene variants on a range of health outcomes and establish how these associations can be modified using combined dietary strategies.

Nutrigenetics: Personalised nutrition: Inter-individual variability: ApoE and apoA5 genotypes: Perilipin genotype

Nutrigenetics refers to the interaction between genetic make-up and dietary components to influence metabolism, health status and risk of diet-related diseases. This interaction is complex, with the influence of genotype on phenotype known to be affected by numerous environmental components, including diet (Fig. 1). Similarly, the influence of altered dietary composition on physiological processes and health status is in large part determined by an individual's genetic make-up, which can impact on the digestion, absorption, metabolism and partitioning, and cellular responsiveness to dietary components. Although a relatively new area of research, it is also recognised that genotype determines food choice, appetite and satiety, and therefore nutrient intake[1,2].

In addition to providing considerable mechanistic insight into the aetiology of disease and the influence of nutrition on metabolic processes, the aim of ongoing nutrigenetics research is to ultimately use genetic profiling for the earlier detection of disease risk and the personalisation of dietary recommendations provided to individuals or population subgroups (Fig. 2). It is hoped that such an approach, along with increasing consumer motivation to adapt lifestyle changes, will increase the physiological benefit afforded to the individual.

Abbreviations: GWA, genome-wide analysis; PLIN, perilipin; SNP, single-nucleotide polymorphisms.

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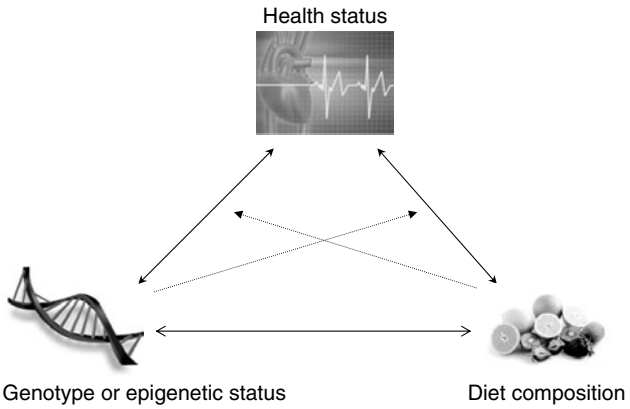

Fig. 1. Overview of nutrigenetic interactions.

However, with increasing availability of published data comes the realisation of apparent inter-study inconsistencies in the strength and direction of observed genotype–diet–phenotype associations and the complexity of nutrigenetic interactions, with a large number of environmental and physiological factors and other gene variants (epistatic interactions) influencing nutrigenetic associations[3–6].

Here, using a number of gene variant–nutrient interactions relevant to CHD as examples, in particular the apoE genotype, which to date represents the most-widely-investigated single nucleotide polymorphisms (SNP), the complexity of nutrigenetic interactions will be addressed along with some insights into steps that need to be taken in order to progress this area of research into a public health tool.

Approaches for identifying genotype–diet–phenotype associations

Linkage studies and genome-wide association studies

A variety of tools and models are available in nutrigenetics research, each with their particular strengths and limitations. Segregation analysis and linkage studies in family groups have led to the identification of the gene loci associated with numerous Mendelian diseases such as Huntington's disease and cystic fibrosis[7–10] and have also made some contribution to current understanding of the genetic basis of polygenic disorders such as CVD[11–13]. Over the last 5–10 years the use of genome-wide analysis (GWA) in large cohorts of unrelated individuals, such as the Wellcome Case-Control Consortium, has dramatically increased genomic discoveries. In these studies genetic variation in $\leqslant 80\,\%$ of the human genome is assessed using typically between 100 000 and 1 000 000 marker SNP and information on linkage disequilibrium from the HapMap project[14]. To date, using GWA approaches, $\leqslant 100$ susceptibility gene loci for a range of chronic diseases have been confirmed, identified and replicated[15–21]. Thus far, these studies have contributed little to the understanding of diet–genotype interactions, as most of them have not captured any information on the habitual diet of the study participants. However, current and future application of GWA to cohorts such as the Framingham Heart Study (www.framinghamheartstudy.org), European Prospective

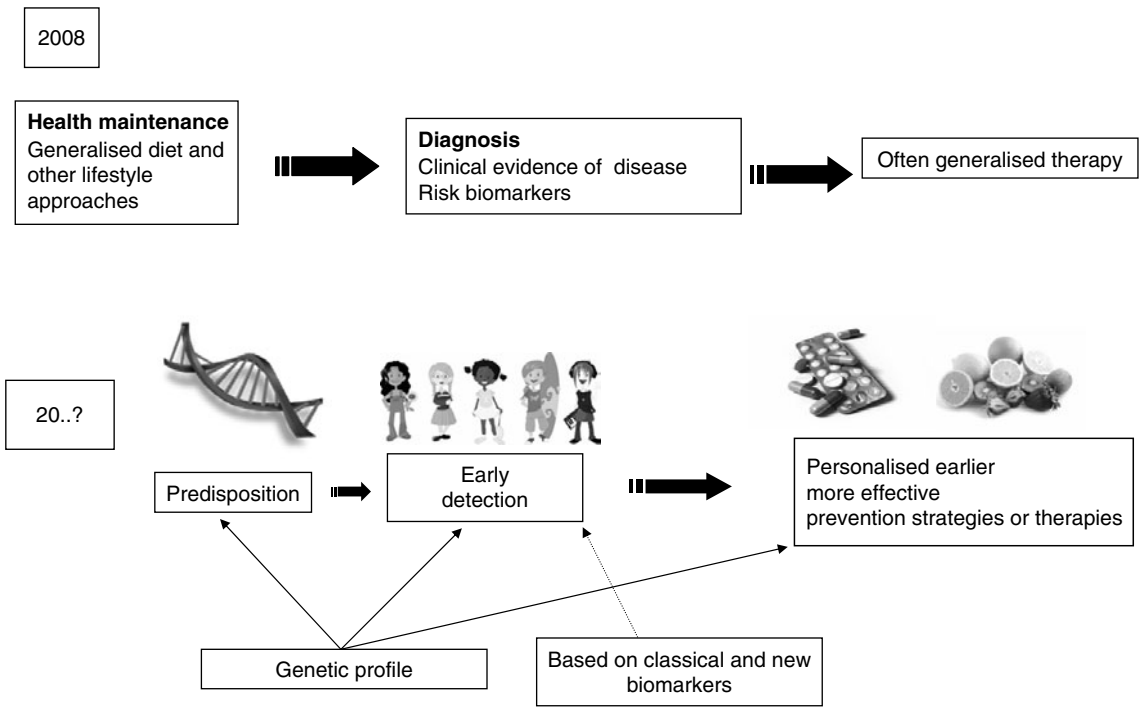

Fig. 2. Scheme of the potential of genetics, nutrigenetics and pharmacogenetics in health maintenance and treatment of diseases. The potential advantages of genotype-based personalised nutrition are: start early; personalised therapy; improved motivation.

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Investigation into Cancer and Nutrition (epic.iarc.fr), the Nurses' Health Study (www.channing.harvard.edu/nhs/) and the Health Professionals Follow-up Study (www.hsph.harvard.edu/hpfs/), for which dietary data are available, is likely to result in substantial advancement in current nutrigenetics knowledge.

Candidate-gene studies

Applying candidate-gene approaches to case–control and cohort studies have thus far provided the vast amount of available information on genetic–disease associations[11,22–28] and how they are influenced by diet and other environmental factors[29–32]. In contrast to the GWA studies, which are not hypothesis driven, traditional candidate-gene studies focus on gene loci for which biological function is known and relevant to the phenotype of interest.

Inconsistencies in genotype–phenotype associations

A comprehensive review of the literature based on both the candidate-gene and GWA approaches demonstrates that many reported associations have failed to be consistently replicated in independent studies[33–35]. The reasons for these inter-study inconsistencies are likely to be multifaceted. Some studies may be under-powered, which can lead to a failure to detect the 'subtle' physiological impacts of a particular gene variant, or provide an imprecise estimate of the size effect. Furthermore, emerging evidence indicates that an array of physiological, dietary or other lifestyle factors impact on the penetrance of a particular gene variant and result in a change in the size of the genotype effect. Gaining an understanding of these complexities in order to be able to predict the likely impact of genetic variation in particular population subgroups represents a major challenge.

Inconsistencies in findings using the candidate-gene approach: lessons from apoE genotype

To date, the most-widely-investigated common SNP–disease association is the relationship between the apoE ε (ε2, ε3, ε4) genotype and CHD risk. ApoE was first described as a component of lipoproteins and mediator of lipoprotein synthesis, circulatory metabolism and their receptor-mediated removal from the circulation[36]. In recent years numerous additional roles have been described, including its role as an anti-inflammatory and antioxidant agent[30,32,37–40]. Globally, the apoE allelic distribution shows substantial variation. Approximately 65% of Caucasian populations are homozygous ε3/ε3, 19% ε3/ε4, 10% ε2/ε3, 4% ε2/ε4, 2% ε4/ε4 and 0·5–1% ε2/ε2[41]. In Europe there is a geographic gradient, with 2-fold higher prevalence of the ε4 allele in northern Europe compared with southern Europe[42], which may contribute to the North–South differences in CHD incidence[43,44].

Over the last three decades numerous studies using both clinically- and angiographically-defined CHD end points have investigated the impact of apoE genotype on CHD risk. These studies have been summarised in three meta-analyses[45–47]. Data from fourteen published observational studies were summarised in the first of the meta-analyses, with carriers of the ε4 allele having an overall OR for CHD of 1·26 (95% CI 1·13, 1·41) and a non-significant OR of 0·98 (95% CI 0·85, 1·14) evident in ε2 carriers[47]. This finding is in agreement with a more recent meta-analysis that includes data from 15 492 CHD cases and 32 965 controls. Overall OR of 1·42 (95% CI 1·26, 1·61) and 0·98 (95% CI 0·66, 1·46) were observed in ε4 and ε2 carriers[46]. In the most recent and comprehensive analysis, which included 121 studies (37 850 cases and 82 727 controls), a more modest effect of the ε4 allele and a protective effect of the ε2 allele is reported, with OR of 1·06 (95% CI 0·99, 1·13) and 0·80 (95% CI 0·70, 0·90) respectively[45]. Examination of individual studies included in these meta-analyses demonstrates the extent of heterogeneity in the observed associations. In the second of the meta-analyses it was reported that mean OR values derived from the individual studies ranged from 0·68 to 4·35 when comparing risk in ε4 carriers compared with the wild-type E3/E3 genotype[46].

Physiological mediators of apoE genotype–phenotype associations

Although a comprehensive review of the physiological determinants of apoE genotype–disease associations is lacking, there is evidence to suggest that gender, age and body weight may have an impact. Data from the Framingham Offspring Study is suggestive of a divergent penetrance of the apoE2 genotype in females compared with males[48–50]. In the prospective 15–20-year follow up from examination 1 (1971–8) to examination 5 (1991–4) OR of cardiovascular events of 1·79 (95% CI 1·15, 2·77) 1·63 (95% CI 1·13, 2·34), 0·79 (95% CI 0·42, 1·48) and 1·56 (95% CI 0·99, 2·45) were reported for male E2, male E4, female E2 and female E4 carriers respectively compared with their wild-type E3/E3 reference group[49] (Table 1). In a cross-sectional analysis conducted at examination 6 (1995–8) no impact of apoE genotype on carotid stenosis was evident in males. In contrast, a significant protective effect of the ε2 allele was observed in females, with 51% lower incidence rates relative to the wild-type E3/E3 genotype (Table 1)[48].

Available data are also highly suggestive of an attenuating effect of apoE genotype according to age, with a lack of association in older cohorts[51–55]. For example, in the Helsinki Sudden Death Study, which conducted lesion staining of the coronary arteries of 700 individuals, significant age × genotype interactions were observed ($P = 0·027$), with a significant impact of genotype only in the <53 years age-group ($P = 0·0085$)[52]. The reason for this reduction in size effect of genotype with age is likely to be because age is associated with an accumulation of environmental influences[56] and an overall multi-faceted higher-risk phenotype, which may mask the relatively-modest physiological impact of the ε4 allele. Furthermore, the lessening of the genotype size effect with age may reflect the fact that individuals represented in this cohort may be relatively insensitive to the effect of the apoE

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Table 1. The adjusted OR for cardiovascular events in the Framingham Offspring Study according to apoE genotype in males and females (adapted from Elosua *et al.*[48] and Lahoz *et al.*[49])

Prospective study	*n*	Total events*	OR1†	95% CI	*P*	OR2‡	95% CI	*P*
Males								
E3	1097	139	–			–		
E2	216	40	1·65	1·10, 2·50	0·017	1·79	1·15, 2·77	0·010
E4	355	66	1·61	1·15, 2·27	0·006	1·63	1·13, 2·34	0·009
Females								
E3	1097	74	–			–		
E2	216	13	0·75	0·40, 1·38	0·354	0·79	0·42, 1·48	0·456
E4	355	34	1·54	1·00, 2·38	0·052	1·56	0·99, 2·45	0·054
Cross-sectional study	*n*	% with ⩾25% carotid stenosis§	OR1‖	95% CI	*P*	OR2¶	95% CI	*P*
Males								
E3	874	23·8	–			–		
E2	169	26·0	1·24	0·79, 1·94	NS	1·22	0·77, 1·95	NS
E4	272	27·6	1·25	0·90. 1·75	NS	1·26	0·89, 1·78	NS
Females								
E3	908	16·0	–			–		
E2	204	10·3	0·54	0·33, 0·87	<0·05	0·49	0·30, 0·81	<0·05
E4	296	17·9	1·26	0·87, 1·83	NS	1·24	0·84, 1·83	NS

E3, E3/E3; E4, E3/E4 + E4/E4; E2, E2/E3 + E2/E2.
*Events in the subsequent 15–20 years, where events are defined as the presence of CVD, which includes CHD (myocardial infarction, angina pectoris, coronary insufficiency, coronary death), stroke, peripheral vascular disease and congenstive heart failure.
†Adjusted for age only.
‡Further adjusted for diabetes, smoking, systolic blood pressure, BMI, left ventricular hypertrophy and use of oestrogens in women.
§Measured in the internal carotid artery.
‖Adjusted for age and familial correlation only.
¶Further adjusted for diabetes, smoking, systolic blood pressure, hypertension treatment, BMI, menopausal status and use of oestrogen-replacement therapy for women.

genotype, with particularly-sensitive individuals suffering from premature mortality not represented.

It is likely that the observation of a greater effect of apoE genotype in normal individuals *v.* overweight individuals[57] is also attributable to the masking effect of the obesity phenotype on apoE genotype–CHD associations.

Behavioural mediators of apoE genotype–phenotype associations

The apoE genotype interacts with diet and other behavioural factors to influence risk of disease. Numerous environmental factors have been shown to influence the effects of apoE genotype on both coronary risk and risk of age-related cognitive decline, including exercise[58,59] alcohol intake[60,61] smoking status[32,62] and dietary fat composition[29], and the interactions have been recently reviewed[30,39].

A limited number of epidemiological studies have examined apoE genotype–dietary fat–phenotype associations. In a Costa Rican case–control study genotype–saturated fat interactions were found, with the impact of a high-saturated-fat diet on myocardial infarction risk and LDL-cholesterol more evident in the presence of the ε2 and ε4 alleles[63]. Similar greater responsiveness of LDL-cholesterol to saturated fat in individuals with the apoE4 genotype was evident in an initial analysis of a subsample (*n* 132) of the EPIC Norfolk cohort[64]; however, this association in E3/E4 and E4/E4 subgroups was not found to be replicated in a subsequent more comprehensive analysis (*n* 22 915)[65].

A review has been conducted of a number of intervention trials that have examined the impact of dietary total fat, saturated fat and cholesterol content on blood lipids according to apoE genotype[29]. The results from these trials are highly variable, with many failing to report a significant genotype–diet interaction. Variable intervention lengths, dietary manipulations and subject groups are likely to explain, to a large extent, the lack of consistency. Furthermore, the majority of these studies were not designed to examine nutrigenetic interaction, with genotyping being conducted retrospectively as an afterthought. As a result many of the studies were underpowered to detect inter-genotype difference in responses, with the distinct possibility that a failure to detect significance is attributable to small group sizes in the rare allele genotypes rather than a lack of a 'real' biological effect.

Of the eleven (of thirty-six studies) that demonstrated significance, six included more than fifty participants, with an additional study that included forty-five participants (fifteen each in E3/E3, E3/E4 and E4/E4 subgroups) prospectively recruited on the basis of apoE genotype[66]. In this latter study reductions in LDL-cholesterol of 5%, 13% and 16% for E3/E3, E3/E4 and E4/E4 individuals respectively were reported following 8 weeks of intervention with a modified National Cholesterol Education Programme diet.

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Thus, available data are suggestive that individuals with the E4 genotype (25% of the UK population) may represent a large population subgroup that is particularly sensitive to dietary total and saturated fat and should be specifically targeted with advice to reduce overall consumption. However, there is great need to consolidate existing analysis using meta-analytical approaches (although variation in study design makes this task difficult) and to conduct adequately-powered trials with prospective recruitment by genotype and detailed analysis of the blood lipid profile in order to conclusively address this wide public health issue.

In addition, recent evidence is suggestive that individuals with the apoE4 genotype are more sensitive to the lipid modulatory effects of the fish oil fatty acids EPA and DHA. Although there are numerous well-described cardioprotective actions of these fatty acids[67,68], increases in LDL-cholesterol in the 5–10% range are commonly evident following high-dose (>2 g/d) EPA + DHA intakes[69,70]. In an initial study conducted in individuals with an atherogenic lipoprotein phenotype retrospective genotyping has indicated that the LDL-cholesterol-raising effects observed following supplementation with 3 g EPA + DHA/d were associated with an apoE4 genotype[71,72]. Two further studies with prospective recruitment according to genotype have: (a) reconfirmed this association; (b) indicated that it is the DHA rather than EPA that is the hypercholesterolaemic agent; (c) highlighted no genotype × LDL-cholesterol interaction at intakes of <2 g EPA + DHA/d. Modest 3–4% increases in LDL-cholesterol were found to be evident in both E3 and E4 subgroups following supplementation for 8 weeks at doses of 0·7 and 1·8 g EPA + DHA/d[73](E Olano-Martin, E Anil, MJ Caslake, CJ Packard, D Bedford, G Stewart, D Peiris, CM Williams and AM Minihane, unpublished results).

Overall, it appears that with intakes at the current UK recommendation of 450 mg EPA + DHA/d there is little evidence of apoE genotype-mediated differences in the LDL-cholesterol response. However, at intakes in the region of those prescribed as hypotriacylglycerolaemic agents (2–4 g/d[74]) EPA-rich oil rather than DHA-rich oil may afford greater cardiovascular benefits in individuals with an E4 genotype, as a result of the LDL-cholesterol-raising effect of DHA.

Perilipin genotype and obesity risk

Adipocyte-derived perilipin (PLIN) is a phosphoprotein that coats intracellular lipid droplets. It has emerged as a key regulator of adipose tissue TAG metabolism, hormone-sensitive-lipase-mediated lipolysis and body fat accumulation[75–77]. In experimental animals PLIN knock-out is associated with increased basal lipolysis, leanness and resistance to diet-induced obesity[78] and in human subjects PLIN levels are elevated in obese individuals[79].

With the rising global burden of obesity and over one billion individuals worldwide being either overweight or obese identification of genetic determinants of body-weight regulation and response to intervention is becoming a highly-active area of nutrigenetic research. Although the PLIN gene locus has not been associated with obesity incidence in GWA studies, evidence from candidate-gene studies indicates that it may be an important factor determining obesity risk and responsiveness to weight-loss programmes. The heterogeneity of these associations reported in the literature provides another insightful example of the complexity of genotype–phenotype associations.

Physiological mediators of perilipin genotype–phenotype associations

A recent review has indicated that gender may be an important determinant of the penetrance of the PLIN genotype[5]. In a Spanish adult population OR for obesity of 0·58 and 0·56 were evident in female carriers of the PLIN1 and PLIN4 rare alleles, with no effect of genotype on BMI or waist:hip ratio in men[80]. Although no impact of these particular SNP was evident in a US cohort, PLIN5 and PLIN6 SNP have emerged as significant predictors of percentage body fat and waist circumference in females only, with 7–11% higher percentage body fat and waist circumference in the homozygous rare allele *v.* wild-type carriers[81]. In a recently published analysis of the impact of PLIN genotype on postprandial TAG metabolism both PLIN1 and PLIN4 rare alleles were shown to be associated with a more effective postprandial TAG clearance[82]. However, no gender × genotype effects were evident.

Perilipin genotype and response to dietary and pharmacological interventions

Research in this area is currently limited to a small number of studies, with available evidence suggesting that rare allele carriers of PLIN4 are resistant to weight loss following dietary restriction and are less prone to the weight gain typically associated with the administration of the insulin-sensitising glitazones[83,84]. Furthermore, an observational study has indicated that the genotype–diet associations may be gender specific[85]. In Asian women, but not men, the PLIN4 genotype was shown to influence the association between saturated fat and insulin-resistance measures (homeostatic model assessment of insulin resistance), with a deleterious impact of high saturated fat only evident in minor allele homozygotes[85]. Thus, early indications are that the PLIN4 genotype may be an important determinant of the response of adiposity measures (and its related phenotype) to behavioural changes. However, much more evidence is needed in order to draw firm conclusions.

Nutrigenetics and postprandial lipaemia

The extent and duration of the postprandial TAG response is recognised to be an important determinant of CHD risk[86–89], with ever-increasing population incidence, given its strong association with excess body weight. The impact of an exaggerated postprandial lipaemic response appears to be more evident in women relative to men. In the Copenhagen City Heart Study adjusted hazard ratios of myocardial infarction for women and men of 5·4 and

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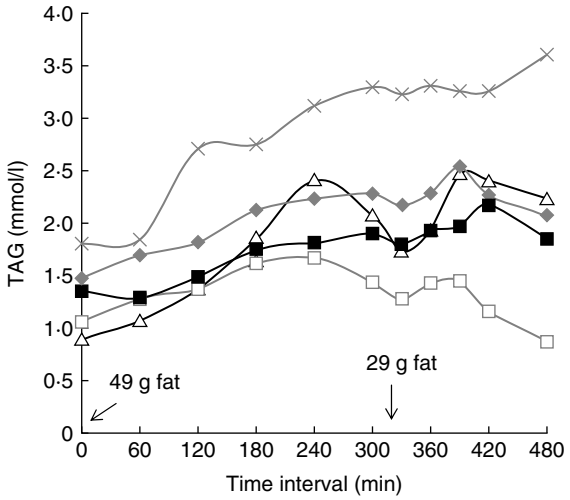

Fig. 3. Example of the heterogeneity in response in plasma TAG levels following standard fat-containing meals. The plot represents the postprandial TAG response to a standard fat-containing breakfast (49 g fat, time 0 min) and lunch (29 g fat, time 330 min) for five individuals chosen randomly from the database of >200 individuals. Blood samples were taken at hourly intervals up to 8 h post breakfast. (Data from AM Minihane, KG Jackson, JA Lovegrove and CM Williams, unpublished results.)

2·4 were evident when comparing non-fasting TAG levels of <1 mmol/l with levels of >5 mmol/l[88]. Pathological effects of postprandial TAG are thought to be a result of the ability of TAG-rich lipoprotein remnants to penetrate and sequester cholesterol into the arterial intima, along with an indirect effect of TAG-rich lipoprotein particles on HDL and LDL metabolism, thrombosis and endothelial function.

Population TAG responses are known to be highly heterogeneous (Fig. 3). In addition to rare gene variants and their associated familial hypertriacyglycerolaemias[90] common polymorphisms in the genes for apo, lipases, transport and other lipid-metabolising proteins modulate postprandial TAG metabolism (for review, see Perez-Martinez *et al.*[91]). One of the most important loci to emerge to date is that of apoA5.

ApoA5 genotype and postprandial lipaemia

ApoA5 was first identified in 2001[92] and has been described as a protein involved in both hepatic TAG synthesis and secretion and the hydrolysis and clearance of TAG-rich lipoprotein from the circulation[93]. Over the last 7 years numerous studies have reported associations between the apoA5 T–1131C and S19W rare alleles (which define the apoA5*2 and apoA5*3 haplotypes respectively) and CVD, and metabolic syndrome and diabetes risk[94–96], and consequently the *apo5* gene has emerged as one of the most consistent loci associated with fasting and postprandial TAG levels[28,95].

Six studies relating apoA5 genotype and postprandial TAG metabolism have been published thus far, with evidence that the apoA5*2 and apoA5*3 haplotypes are associated with an approximately 30–60% higher postprandial TAG response relative to the wild-type apoA5*1 haplotype, defined by −1131T and S19 alleles[28,97–101]. Five of these investigations have been conducted in young males and ethnically-homogenous cohorts[97–101]. Thus, little information on gender, age and ethnicity × genotype interaction can be derived from these studies. However, the most recently published study, which included 153 males and 109 females, provides strong indications of an impact of gender on the association between the −1131C allele and apoA5*2 haplotype and TAG metabolism (Fig. 4)[28]. A significant impact of genotype was only evident in males (corrected for baseline levels; $P = 0{\cdot}007$). It is speculated that this finding may be in part attributable to the known impact of oestrogen on many stages of TAG-rich lipoprotein metabolism, which may mask the deleterious impact of the apoA5 mutant.

In accordance with other gene variants that modulate lipoprotein metabolism, there is some evidence that dietary fat composition influences the 'size effect'; of the apoA5 T–1131C variant on TAG metabolism[95]. An analysis of data from the Framingham cohort indicates that the association is modulated by dietary PUFA composition[102]. Fish oil fatty acids are the most potent known dietary hypotriacylglycerolaemic agents, with 20–40% reduction typically observed following high-dose intakes (2–4 g EPA + DHA/d)[72]. Given that there is considerable mechanistic overlap between fish oil action and apoA5 modulation of TAG metabolism, with fish oils reducing hepatic TAG output and enhancing LPL activity, it is highly likely that EPA + DHA intake would influence apoA5–TAG associations and in part negate the negative effects in those with the apoA5*2 and apoA5*3 haplotypes. This interaction is worthy of investigation.

Investigations of the impact of specific genotypes, haplotypes and genotype combinations on postprandial TAG metabolism are logistically difficult studies to conduct, as they require volunteers to provide regular blood samples typically up to 8 h post test meal. As a result cohorts are often small (<100 individuals), making meaningful analysis of genotype–phenotype associations difficult, in particular for rarer alleles. Furthermore, subgroup analysis according to gender, age etc. is often impossible. Combining existing smaller cohorts may allow more detailed analysis to be conducted. However, this approach is often difficult because of variations in study protocol, in particular test meal composition. There is a strong justification for the standardisation of postprandial protocols in order to allow cross-study comparisons and amalgamation of datasets.

Future needs in nutrigenetic research

Nutrigenetics is undoubtedly a relatively new area of nutritional science, with research in its relatively infancy. Although the evidence base in nutrigenetics is growing, with sufficient data available to provide a 'proof of principle' of its potential utility in public health, this area currently suffers from a lack of consistent findings.

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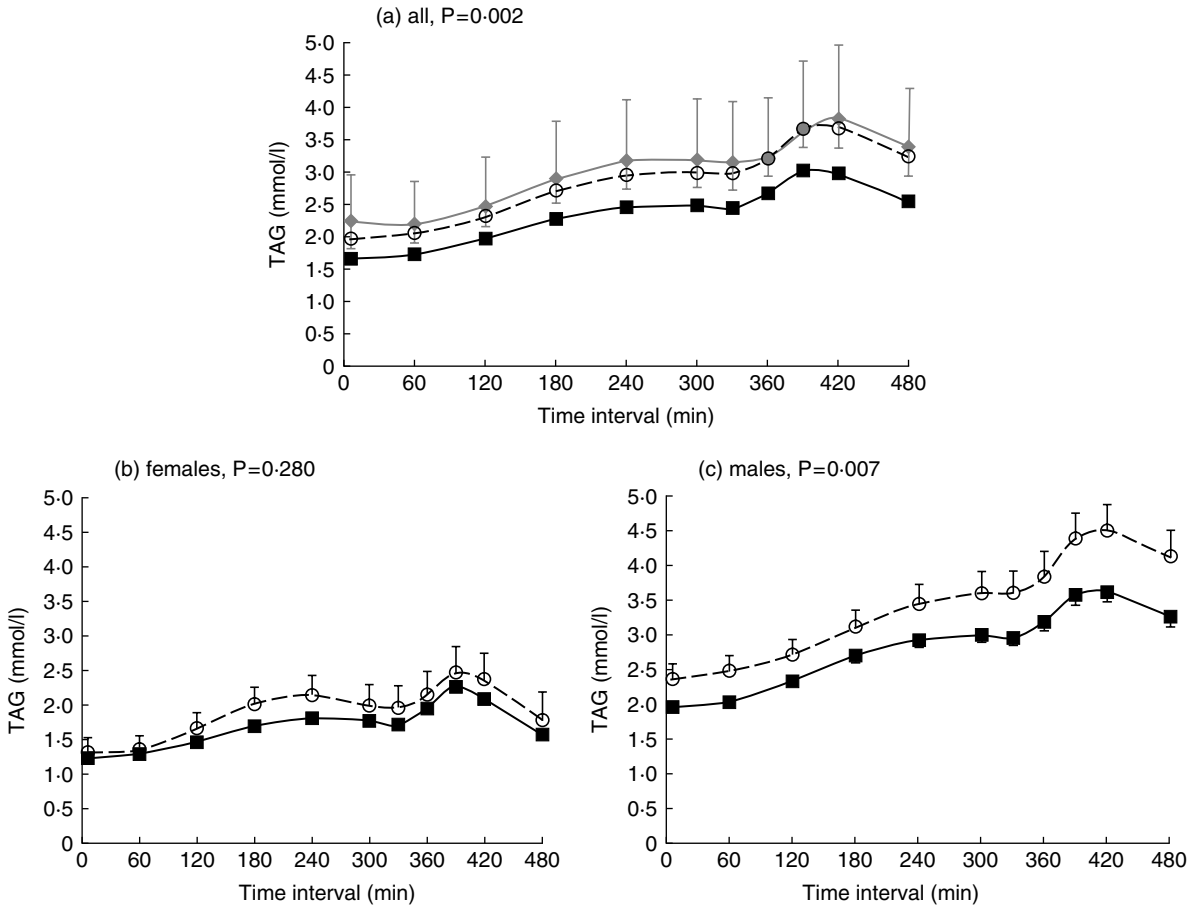

Fig. 4. Impact of apoA5 T–1131C genotype on the postprandial plasma TAG response. (a) All subjects: (■–■), TT (*n* 214); (○– –○), TC (*n* 42); (–◆–), CC (*n* 3); $P = 0{\cdot}002$. (b), Females: (■–■), TT (*n* 92); (○– –○), TC (*n* 16); $P = 0{\cdot}280$. (c) Males (■–■), TT (*n* 122); (○– –○), TC (*n* 26); $P = 0{\cdot}007$. Values are means with their standard errors represented by vertical bars. (Adapted from Olano-Martin *et al.*[28].)

In observational studies a lack of consistency may be a result of small group size, experimental error associated with inaccurate assessment of the phenotype of interest or, more commonly, a result of inaccuracies and bias associated with the recording of dietary intake. It is highly likely that the reliability of dietary information may depend on factors such as age, ethnicity, gender and health status, which could introduce a considerable amount of error in the assessment of genotype–diet–phenotype–associations. The quantification of biomarkers of dietary exposure in accessible biofluids holds great potential as a dietary assessment tool. To date few reliable dietary biomarkers are available, with the exception of a number of micronutrients and specific fatty acids (e.g. EPA and DHA and *trans*-fatty acids). Metabolomic profiles in biologically-accessible tissues holds some potential. However, it is difficult to assess at present its future role in the assessment of dietary exposure.

As evidenced in the present review, perceived inconsistencies between studies often reflect the impact of physiological (e.g. age, gender, ethnicity, health status) and environmental factors on the direction and size of genetic associations, and consideration of these apparent inconsistencies can be very insightful and provide information about the relative importance of gene variants in particular population subgroups. A consensus relating to standardisation in the capture of such information would greatly assist in study interpretation and amalgamation of datasets to allow larger meta-analyses.

Human intervention studies overcome, in part, inaccuracies in dietary assessment, as the investigator is supplying a known quantity of the food or food component of interest. However, in the past many studies in this area have been of dubious quality, with short intervention periods, small numbers of participants and retrospective genotyping (as these trials were designed for purposes other than to study nutrigenetic interactions) resulting in inadequate power to detect subtle nutrigenetic interactions. Prospective recruitment by genotype, with equal numbers in genotype subgroups of interest overcomes this problem. Such approaches are however expensive and logistically difficult to conduct and should be reserved to validate nutrigenetic interactions reported in observation trials or in intervention studies with retrospective genotyping.

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Furthermore, much more attention needs to be given to identifying the functional gene variants and the metabolic basis for nutrigenetic interactions. Current candidate-gene or GWA studies provide information on which SNP are associated with, and are in linkage disequilibrium with, a particular phenotype, but do not necessarily identify the precise SNP. Such information, along with adding authenticity to the observed associations, is essential in order to help identify diet and other behavioural strategies that may counteract the 'at risk' genotype. Stably-transfected cells lines and targeted-replacement animal models have proved useful in this context. For example, traditionally the physiological basis of the apoE genotype effect on CVD risk and risk of age-related cognitive decline has been thought to be its LDL-cholesterol-raising effect. However, using these models recent data are suggestive that the ε4 allele is also associated with a pro-inflammatory and pro-oxidative state[38,39].

Alongside basic research there is a great need to make the most of existing data using a variety of traditional statistical and mathematical methods along with newly-developing bioinformatic techniques. Currently, a very reductionist approach is often taken, examining associations between single loci, single dietary components and specific phenotypes. However, this approach must feed into a more holistic scenario, examining the interactive effect of genetic and environmental components on health. Each individual possesses potentially hundreds (or more) of gene variants that may influence metabolism and health status, the penetrance of which may be modified by many physiological, dietary and other behavioural variables. Although epidemiological studies and meta-analysis in >100 000 individuals can provide some interactive information, this holistic overview can only be fully achieved by mathematical modelling and bioinformatic technology. Examples of this type of analysis are already appearing in the literature[24,103,104].

In conclusion, genetic profiling is becoming increasingly cost effective and high throughput[105] and holds great potential as a means of estimating future disease risk and personalisation of strategies to effectively reduce disease risk. However, it is currently not ready to be used as a widespread public health strategy for chronic disease management. A much more comprehensive understanding of the penetrance of genotypes in population subgroups, the identity of the mechanistic basis of pathological variants and the impact of the combined effects of multiple variants and their interaction with environment is needed. Alongside the progression of scientific evidence, attention should also be paid to some of the surrounding issues such as the ethics and consumer acceptability of genetic profiling, issues that need to be resolved before this potentially valuable public health tool can be used more widely.

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