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Review Article

Personalised nutrition: status and perspectives

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Personalised, genotype-based nutrition is a concept that links genotyping with specific nutritional advice in order to improve the prevention of nutrition-associated, chronic diseases. This review describes the current scientific basis of the concept and discusses its problems. There is convincing evidence that variant genes may indeed determine the biological response to nutrients. The effects of single-gene variants on risk or risk factor levels of a complex disease are, however, usually small and sometimes inconsistent. Thus, information on the effects of combinations of relevant gene variants appears to be required in order to improve the predictive precision of the genetic information. Furthermore, very few associations between genotype and response have been tested for causality in human intervention studies, and little is known about potential adverse effects of a genotype-derived intervention. These issues need to be addressed before genotyping can become an acceptable method to guide nutritional recommendations.

Nutrigenetics: Nutrigenomics: Nutritional recommendations: Genotype: Disease risk

The role of nutrition as a major factor in the development and prevention of chronic diseases has received increasing attention on the part of the media, the public, industry and the regulatory agencies in most countries (Joint WHO/Food & Agriculture Association Expert Consultation, 2003). The food industry has responded to this growing awareness by creating new products, in particular functional foods, that promise a reduction in the level of risk factors for chronic disease.

More recently, this development has converged with rapid progress in the field of genome research. The concept of a personalised, genotype-based nutrition that might provide individuals with a high risk of diseases such as diabetes, atherosclerosis and cancer with specific nutritional advice, thereby maximising the efficacy of preventive intervention, has been discussed (Davis & Milner, 2004; Kaput & Rodriguez, 2004; Ordovas & Corella, 2004). Moreover, companies have been founded that offer nutritional advice based on the genotyping of polymorphisms in a limited number of genes such as *MTHFR*, *CYP3A4* and *PPARγ*. As this development has received controversial responses from both the media and the scientific community, we believe that an expert statement is required on the validity of the concept of health-targeted, personalised nutrition and on its present status and future perspectives.

The concept of a personalised nutrition

It has to be noted that the concept of a nutrition adapted to specific personal parameters is not new. Persons distinguished

Abbreviations: SNP, single-nucleotide polymorphism.

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by age or by a particular physiological status – for example, infants or pregnant women – have different nutritional needs. Moreover, patients with allergies or chronic diseases, such as diabetes, dyslipoproteinaemia or liver disease, require special diets. It follows that nutritional recommendations for the general population need further differentiation for specific subgroups. A new development, however, is the possibility of genetic testing linked with nutritional advice as a result of a risk–benefit analysis of dietary components on an individual basis (Hesketh *et al.* 2006).

Chronic diseases represent the phenotype of altered gene expression, as a result of interactions between environmental factors and genetic make-up (i.e. the inherited collection of 'susceptibility' and 'protective' genes). These interactions are conceptualised in the 'health pendulum' (Fig. 1), which attempts to summarise the major influences, including genetic make-up, that determine health outcomes. It is therefore a reasonable assumption that a knowledge of the interactions between genotype and diet (and other lifestyle factors) will be of major help when assessing disease risk and when initiating preventive measures. In addition, available data suggest that the complex disease-promoting or disease-preventing effects of a specific diet may depend on genetic make-up (Davis & Milner, 2004; Kaput & Rodriguez, 2004). Thus, in theory, the concept of personalised nutritional recommendations that are based on genetic data should help to fine-tune the prevention of nutrition-associated diseases. Whether this will work in practice is, however, unknown and will depend on the predictive precision of the genetic information for phenotypic outcome, on the robustness of gene–diet–disease relationships and on the public's acceptance of the concept.

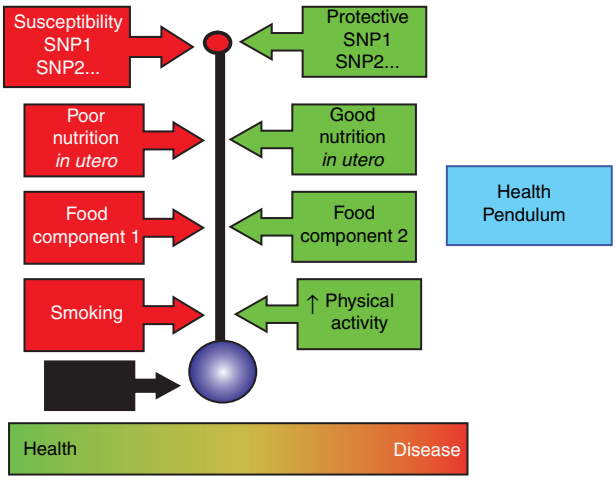

Fig. 1. For a given individual, the position along the health-disease continuum from which the pendulum is suspended depends on genetic make-up (indicated by the inherited collection of 'susceptibility' and 'protective' genes). Nutrition *in utero* and postnatal lifestyle interacts with genetic make-up to further modify the risk; i.e. each of these factors pushes the individual's pendulum to the right or the left. The net effect of these 'forces' will determine whether an individual is, or is not, healthy. Factors that enhance risk are shown in red, whereas those reducing risk appear in green. For emphasis, time is shown in a black box and has an arrow pointing to the right to indicate that, for most common non-communicable diseases, risk increases with age. SNP, single-nucleotide polymorphism. (Adapted from Mathers, 2002.)

Genotype-dependent effects of nutrients in monogenic diseases

There are several examples of monogenic disorders that require dietary intervention. Perhaps the most common and best known example is lactose intolerance. Most mammals lose the ability to hydrolyse lactose in adulthood. In Northern Europe, however, a variant allele of the lactase gene, which results in a continued expression of lactase into adulthood, originated about 9000 years ago (Enattah *et al.* 2002). Another well-known example is phenylketonuria, which is caused by loss-of-function mutations in the gene encoding the enzyme phenylalanine-4-monooxygenase (Levy, 1999). If newborn infants homozygous for this genotype do not adhere to a phenylalanine-reduced diet, the amino acid is converted to a ketone that interferes with neural development and causes mental retardation. Other examples of genotype-dependent dietary effects are the familial hyperlipidaemias, in which the dyslipoproteinaemia may be diet-sensitive or diet-insensitive, depending on the genotype (Loktionov *et al.* 2000; Ordovas, 2004).

These examples provide proof of the concept that nutritional effects may depend on a certain genotype. It needs to be emphasised, however, that they do not prove the need to know the *genotype*: in monogenic disorders, knowledge of the *phenotype* is usually sufficient for dietary intervention. This is in contrast to complex diseases, in which multiple lifestyle and genetic factors cause a high degree of heterogeneity in the pathophysiology, course and secondary complications of the disease.

Status of the concept of personalised nutrition in complex diseases

There are three aspects from which this topic can be viewed. The first focuses on the associations of particular genetic variation with the risk of diet-related chronic disease. In contrast with monogenic disorders, the genetic basis of polygenic, complex diseases such as diabetes, hypertension or hypercholesterolaemia remains poorly understood. There are numerous single-nucleotide polymorphisms (SNP) that have been found to be associated with an increased disease risk, and are therefore thought to be involved in its pathogenesis. These associations have, however, often been inconsistent and are rarely supported by data on the functional consequence of the SNP (Hirschhorn *et al.* 2002). In some instances, the same genotype shows opposing effects on a biological parameter in different populations, for example the vitamin D receptor genotype on bone mass (Cusack & Cashman, 2003). Furthermore, SNP identified to date each explain only a small portion of the genetic basis of complex diseases, and the number of genes modulating disease risk in a single individual appears to be higher than initially thought.

A second aspect from which to view the issue of personalised nutrition is to extend the SNP–disease link to include a dietary factor. In a few instances, a specific interaction between a gene variant and nutritional parameters has already been described. Variants of genes involved in the metabolism of xenobiotics, such as *N*-acetyltransferase and glutathione-*S*-transferase, have been found to be associated with higher or lower cancer risks in individuals with a higher consumption of well-done meat or cruciferous vegetables, respectively

(Deitz *et al.* 2000; Seow *et al.* 2002; Joseph *et al.* 2004). A variant of the manganese-dependent superoxide dismutase gene has been reported to be associated with an increased risk of breast cancer in women with a low intake of fruits and vegetables (Ambrosone *et al.* 1999; Cai *et al.* 2004), and of aggressive prostate cancer in men with low plasma antioxidant status (Li *et al.* 2005).

Much stronger evidence that genetic make-up can determine the biological response to nutrients is provided by inbred mouse strains. Here, the sensitivity to a high-fat diet is very strain-specific (Nishina *et al.* 1993). Moreover, in obese mouse strains, chromosomal regions have been identified that confer dietary fat-dependent susceptibility for diabetes (Plum *et al.* 2002). This finding – if applicable to the human situation – suggests that it is possible to identify individuals with a high risk of developing diabetes who might benefit specifically from a fat-reduced diet.

The available data indicate two major problems for the concept of genotype-based intervention. First, the consequences for health of carriage of a particular SNP may be complex, with both beneficial and detrimental effects on different diseases. For example, homozygosity for the TT variant of the C677T SNP in the methylenetetrahydrofolate reductase (*MTHFR*) gene results in reduced activity of the encoded enzyme, raised plasma homocysteine concentrations and an elevated risk of neural tube defects, cardiovascular disease (Strain *et al.* 2004) and possibly osteoporosis (Cashman, 2005). Conversely, individuals carrying the TT version of *MTHFR* appear to have a lower risk of bowel cancer, especially if their folate intake is high and they abstain from high alcohol intake (Sharp & Little, 2004).

Second, the contribution of single SNP to total disease risk is small, usually much smaller than that of conventional risk factors, and can be dependent on the presence of other gene variants (epistasis). For example, the diabetogenic haplotype of the calpain-10 gene increases disease risk by approximately 20 % (Song *et al.* 2004), whereas a family history of diabetes increases the disease risk by a factor of four, and being overweight adds a factor of 4–30-fold (Colditz *et al.* 1995). Associations between plasma triacylglycerol levels and genotype were found only for multisite SNP in the APOA1/C3/A4/A5 cluster but not for single SNP in this region (Payseur *et al.* 2006). Furthermore, the HapK allele of leukotriene A4 hydrolase causes a threefold higher increase in the risk of cardiovascular disease in African Americans than in European Americans, indicating a marked epistatic interaction of HapK with other alleles prevalent in African populations (Helgadottir *et al.* 2006).

Thus, on the basis of the present data, it is concluded that, in complex diseases, the predictive value of a single genotype is small compared with that of the family history of a person or with that of other known risk factors. In addition, evidence of interactions between dietary factors and genotype on disease risk is fragmentary. Nevertheless, it is reasonable to assume that the effects of single diet–gene interactions are largely modified by epistatic interactions, like the effects of single SNP on a disease risk. Consequently, current attempts to derive dietary recommendations based on the genotypes of the few single SNP presently known to be associated with particular complex diseases appear largely experimental. Recently, such tests have, provocatively, been called 'genetic horoscopes' (Russo, 2006).

A third aspect from which to view the subject is, however, to move back from the complex disease itself to specific risk factors for the disease that have a well-established responsiveness to dietary intervention. A simple example would be the higher risk of those carrying the T allele of *MTHFR* for elevated levels of plasma homocysteine when intakes of folic acid are very low (Strain *et al.* 2004). Another example is the higher sensitivity of HDL cholesterol to intake of PUFA in women carrying the −75A allele of *APOA1* (Ordovas *et al.* 2002).

Thus, the three perspectives from which this area can be viewed go from gene–chronic disease links to gene–diet–chronic disease links to gene–diet–risk factor links, each having their own particular challenges. It seems reasonable to assume that the number of genes involved in gene–diet–risk factor links is lower than in gene–diet–disease links (Fig. 2). A focus on gene–diet links with predominant risk factors might therefore be the preferable strategy to introduce genotype-based nutritional advice. Thus, for the time being, personalised nutrition may focus on relatively few genes that regulate key risk factors and that are highly sensitive to diet.

What are the requirements for valid genotype-based nutritional recommendations?

In order to derive recommendations from an individual's genetic profile, the genetic information should predict a robust increase or decrease in disease risk in relation to a specific dietary pattern, food or nutrient intake. In addition, it should be established by solid evidence that the genotype-based intervention indeed reduces disease risk or risk factor levels. Both criteria are difficult to meet, as has become apparent in the last few years.

The genetic basis of complex diseases comprises an unknown number of gene variants. In mouse strains, in which the identification of susceptibility loci by breeding techniques is easier, as many as sixty loci may determine body weight and adiposity in different strains, and as many as 10–20 may be present in a single inbred strain (Wuschke *et al.* 2006). In a worst-case scenario, therefore, it can be estimated that the total number of gene variants responsible for a certain disease may lie in the hundreds, and that of these perhaps 5–20 would have to be present in one individual to modify risk substantially. As high numbers of different combinations of haplotypes are possible, very large study populations are required to investigate the effects of the individual haplotype (Cardon & Bell, 2001). It appears reasonable to predict that only a few genotypes that exert a major influence on disease risk will thus be suitable for genetic testing.

Most of the associations between diet, risk factors for chronic disease and genetics have come from epidemiological studies and, as with conventional nutrition research, such observations need to be verified by dietary intervention studies to provide evidence of causality. At present, no internationally agreed standard exists for the design and interpretation of such studies, and there is thus an urgent need to develop such norms (Kaput *et al.* 2005). A number of issues need to be taken on board. In selecting the sample, a similar number of those carrying the reference sequence and those homozygous or heterozygous for the variant allele will need to be recruited. Each

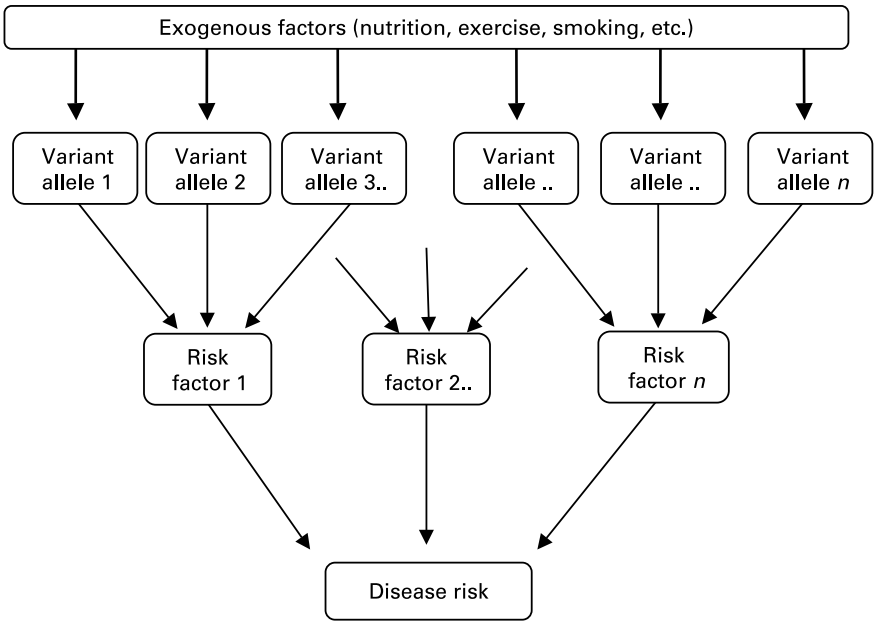

Fig. 2. A simplified model of the complex interaction between nutrition, gene variants, risk factors and disease risk. Risk factors are phenotypic effects of the interaction between nutrition and gene variants, i.e. alterations in serum parameters such as LDL-cholesterol, adiponectin or postprandial glucose level. According to the model, disease risk equals the sum of the numerous effects of variant genes. Monitoring the effects of the variant genes on intermediate risk factors may reduce the complexity of the gene–nutrient interaction, and represents the most realistic option for guiding personalised nutrition.

genetic group should be rotated across each of the dietary interventions. Quite how the data from such intervention studies should be interpreted needs serious consideration. Take a hypothetical example in which a certain genotype in combination with a particular diet leads to a reduction in some undesirable risk factor. If the variation in this reduction is high, due to other genetic and non-genetic biases, one cannot counsel at an individual level with any certainty. One might, however, be able to counsel at a population genetic level. On the other hand, if the variation around the reduction is small, personalised counselling on this diet–gene interaction becomes realistic.

There are, however, two key issues that still need to be addressed. The first is whether the diet in question has adverse effects if certain SNP are present in other genes. Thus, for some individuals, a given dietary lipid profile might have beneficial effects on cholesterol metabolism with SNP*x* in gene A but bad effects for T-cell function with SNP*y* on gene B. Furthermore, a certain risk factor for chronic disease might be significantly improved by dietary pattern A but be adversely affected if some other nutritional change were simultaneously introduced. In effect, we need to be aware that the net benefit of a given nutritional intervention will depend on the sum of several diet–gene–risk factor interactions. It is not safe to assume that an intervention based on a particular genotype–risk factor association will produce a net beneficial response in everyone with that polymorphism.

What future research directions are needed?

Future research will have to provide solid evidence for associations between genotype, diet and disease or risk factor. In addition, it is very important that the benefit of a dietary intervention in carriers of a certain genotype is demonstrated in intervention studies. In that respect, there are some unresolved issues over the set-up of such studies, for example whether assessment of the benefit requires changes in disease outcome or whether surrogate end points or risk factor levels suffice.

Current methodological and conceptual developments in determining genotype–phenotype associations are promising. First, genome-wide genotyping in large cohort studies is becoming feasible (Hinds *et al.* 2005). Furthermore, there is emerging evidence that other variations in the genome, for example epigenetic modifications (Jaenisch & Bird, 2003) and copy-number polymorphisms (Feuk *et al.* 2006; Redon *et al.* 2006), are as important risk predictors as SNP, and that effects of diet may be recorded and remembered through changes in epigenomic markings, resulting in altered gene expression and cell function (Dolinoy *et al.* 2006).

Second, there are expectations that the 'omics' technologies (mRNA expression profiling, proteomics, metabolomics) will identify specific alterations that predict disease risks or the interaction of genetic variation with diet with acceptable accuracy (van Ommen & Stierum, 2002; German *et al.* 2004). These technologies are not, however, without some serious technical and conceptual challenges. mRNA profiling and proteomics are limited by difficulties in obtaining samples from the tissues of interest for studies carried out in human subjects. The metabolomics technologies may eventually provide complete metabolic profiles that will help to more precisely assess the effects of nutrients in a study population, but they are currently still limited in their capacity to identity less abundant metabolites precisely.

A third approach that is currently being developed is the mathematical modelling of the effect of multiple SNP on a biological parameter, such as the modification of plasma cholesterol levels by thirteen SNP (Knoblauch *et al.* 2004). Finally, mouse strains with defined gene variants (congenic

inbred strains or lines with multiple targeted gene variants) that are currently being generated will be useful tools for unravelling the complex genotype–nutrient interactions.

What are the benefits of genotype-based personalised nutrition?

Given that the interaction between a particular allele and a specific dietary exposure leads to some beneficial effect on a risk factor for chronic disease, there are three potential benefits. First, genotyping offers the prospect of starting early in the prevention of the disease, earlier than with non-genetic biomarkers related to disease risk. This is particularly important for diseases in which the development of the pathology and its complications has long latency periods and is essentially irreversible, such as in type 2 diabetes or osteoporosis. Second, the success of a specific and early dietary intervention would save resources by targetting advice and help towards those who would be most likely to benefit. Finally, a potential benefit is that an individual with an elevated disease risk may, once he or she has obtained the genetic information, have a higher motivation to comply with the dietary intervention than when given general advice. It should be noted that this potential advantage is as yet untested and debatable. The possibility cannot be excluded that, in some individuals, knowledge of a genetic predisposition might lead to a fatalistic attitude and a reduced compliance with any intervention.

What are the risks?

In our opinion, the main risk related to genetic testing is that recommendations and decisions may be based on insufficient or even inadequate data, and that other, for example medical history or phenotypic, data receive too low a priority. Genetic data, when obtained with standard procedures, are unambiguous, but the functional consequences are not. For example, if a certain genotype were to predict a particular strong beneficial effect of alcohol consumption on coronary heart disease, would that lead to a recommendation to increase alcohol intake for that individual? Probably not, because such a recommendation would enhance the risk of other diseases such as liver disease, alcoholism and cancer, and may have other adverse social consequences. In this example, the risks of the recommendation are well recognised. In others, however, there is limited information, and it is conceivable that a specific recommendation – or the individual's response to the recommendation – would increase an unknown risk.

Other risks relate to the intrinsic sensitivity of personal data that may be used by 'interested third parties' such as employers, insurance companies and others. These risks can be contained by laws preventing the disclosure of information to third parties and regulating other uses of data and of 'residual' biological samples. Finally, we consider it a risk that tests may be introduced too early, lead to disappointment and have adverse effects on society's view of this emerging, and potentially very exciting, new science.

Will the concept be accepted by society?

The status of plant biotechnology and stem cell research in Europe has taught us that it is becoming increasingly difficult to convince the public of the benefits of new products and procedures that are somehow connected with genes and/or cloning. Resistance towards these techniques has been strong and appears to be growing. The attitude of consumers to genetic testing seems, however, to be at variance with their attitudes to plant biotechnology. According to data from the Eurobarometer survey of 2002 involving 16 500 subjects in the then member states of the European Union, the majority of respondents supported genetic testing for disease (Gaskell *et al.* 2003). To date, no studies have been published that probe differences between genetic testing for a disease and genotyping to predict the probability of response to some dietary intervention.

A final issue to be considered is the capacity of society to deliver 'customised solutions' to personalised nutrition. Even if we could some day identify the ideal diet for a particular individual, effective strategies to deliver this diet remain to be developed. With appropriate help and information, the individual consumer could choose his or her 'personalised' food products at the grocery store, but how to provide families and deliver the personalised food through canteens would be a complicated issue. It is conceivable that, for practical reasons, the customised solutions will be less precisely titrated to the full, individual genomic information, and targetted at families rather than individuals. Thus, personalised nutrition may have a long road ahead of it.

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