

Review Article

Genetic variation and dietary response: Nutrigenetics/nutrigenomics

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Advances in molecular and recombinant DNA technology have led to exquisite studies in the field of genetics and the recognition in a much more specific way, through DNA sequencing, of how unique each one of us is, and the extent to which genetic variation occurs. The importance of the effects of genetic variation has been extensively studied and applied by pharmacologists in drug development and evaluation of drug metabolism and adverse reactions to drugs. In the past two decades, physicians, geneticists, and nutritionists have begun to study the effects of genetic variation and gene–nutrient interactions in the management of chronic diseases, such as coronary heart disease, hypertension, cancer, diabetes and obesity; and the role of nutrients in gene expression. A new era is being ushered in that may be called ‘nutrigenetics/nutrigenomics’. The new genetics has enormous implications for nutrition research both in the prevention and management of chronic diseases. Because families share both genes and environment (in this case, diet), similarity may result from either. Much research has been carried out to define the contribution of each and their interaction in the development of the individual. Knowledge of genetic susceptibility to disease will help identify those at higher risk for disease, as well as their response to diet. The prospect of targeting specific dietary treatment to those predicted to gain the most therapeutic benefit clearly has important clinical and economic consequences, particularly in diseases of high prevalence such as coronary artery disease, hypertension, osteoporosis, and possibly cancer. With the unfolding genomic and technological revolution, continuing investments in research offers unprecedented opportunities to understand disease processes, prevent intrinsic and environmental risks to health and develop new approaches to improve the quality of life worldwide. Furthermore, knowledge of genetic susceptibility to disease will help identify those at higher risk for disease, as well as their response to diet. As a result, there will be a need for the development of novel foods targeted to individuals, families and subgroups within populations. Although the emphasis of new genetics has been on pharmacogenetics, it is the responsibility of the nutrition scientists to expand in parallel the relationship of genetics and nutrition and establish nutrigenetics/nutrigenomics as a major discipline in nutrition in the 21st century.

Key words: chronic diseases, dietary recommendations, dietary response, gene expression, gene–nutrient interaction, genetic variation, nutrigenetics/ nutrigenomics.

Introduction

The interaction of genetics and environment, nature and nurture is the foundation for all health and disease.¹ Nutrition is an environmental factor of major importance. Major advances have occurred over the past 15 years in the fields of both genetics and nutrition. Methodological advances in molecular biology and genetics have facilitated the study of inherited disease at the DNA level, and the study of nutrients at the molecular level. This has led to (i) the development of concepts and research on genetic variation and dietary response (i.e. individuals responding differently to the same diet by having different levels of, for example, serum cholesterol and blood pressure because of genetic variation); and (ii) studies on the evolutionary aspects of diet and the role of nutrients in gene expression (i.e. polyunsaturated fatty acids (PUFA) suppress fatty acid synthase (mRNA) gene expression). In addition to nutrients, non-nutritive dietary phytochemicals, for example phenolic compounds, are being studied for their effects on various aspects of

human metabolism. Nutrigenomics could provide a framework for the development of novel foods that will be genotype dependent for the promotion of health and prevention and management of chronic diseases. In the USA and other countries, general dietary guidelines have been issued for the prevention of chronic diseases. In the development of dietary recommendations, the effects of genetic variation on dietary response have not been considered, despite such evidence.^{2–4}

This paper discusses heritability; genetic variation and dietary response relative to (i) dietary cholesterol and plasma cholesterol levels and (i) dietary sodium and the response of blood pressure; gene–nutrient interactions and their role in

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determining nutritional requirements using folate intake and red-cell folate concentrations as a case in point; the role of nutrients in gene expression, ethnic differences and gene variants; the future of genetic nutrition: nutrigenetics/nutrigenomics; the potential for novel foods; global efforts in genetics and biotechnology; and finally, conclusions and recommendations.

Heritability

Coronary artery disease, hypertension, diabetes, cancer and other chronic diseases in adults tend to aggregate in families, and the risk of relatives is much higher than that in the general population (Table 1).⁵ Because families share both genes and environment, similarity may result from either. Much research has been carried out to define the contribution of each, and their interaction in the development of the individual. Broadly defined, heritability is the proportion of the total variance that can be explained by genes.⁶ Studies in the USA have shown that 50% of the variance in plasma cholesterol concentration is genetically determined.^{7,8} Mongeau determined that 30–60% of the variance in blood pressure is genetically determined;⁹ between 15 and 50% of the variance in fibrinogen, an independent risk factor for coronary artery disease, is genetically determined.^{10,11} Fifteen per cent of the variance was found in the United Kingdom¹⁰ while 50% is the figure among the Swedish population, indicating significant differences between populations.¹¹ Morrison *et al.* in Australia showed that 75% of the variance in bone density is genetically determined.¹² Calculations of heritability are relevant only to the specific population and environment from which information is gathered. Heritability may vary between populations if they differ in the prevalence of the types of genes affecting the disease entity under consideration. Populations therefore should not copy each other's dietary recommendations for the prevention of coronary artery disease or cancer, or any other disease for that matter.

Genetic variation and dietary response

Genetics deals with variation. A fundamental aspect of the genetics approach to disease is an appreciation of human variation: its nature and extent, its origin and maintenance, its distribution in families and populations, its interaction

with environment, and its consequences for normal development and homeostasis.^{1,13,14}

How extensive the genetic variation is depends on how it is measured. At the level of DNA genetic variation is considerable because in every 1000–2000 nucleotides there is a substitution leading to single nucleotide polymorphisms (SNP). Single nucleotide polymorphisms refer to alterations of single bases (adenine, guanine, cytosine or thymine) in the 1.83 m long string of bases that make up human DNA. At the level of protein diversity (that is, variation in the sequence of amino acids) genetic variation is much less. In human beings approximately 30% of loci have polymorphic variants, which is defined as two or more alleles with frequencies of at least 1% or more in the population.

Advances in human biochemical genetics have produced data that suggest considerable biochemical variability within and between human populations.¹ Therefore the relevance of this genetic information for human nutrition is considerable. Variation in nutritional requirements and the interaction of certain nutrients with genetically determined biochemical and metabolic factors suggest different requirements for individuals. This variation (like sex differences) is inborn and needs to be differentiated from variations caused by the life cycle (growth, pregnancy, and old age). Using the tools of molecular biology and genetics, research is defining the mechanisms by which genes influence nutrient absorption, metabolism and excretion, taste perception, and degree of satiation; and the mechanisms by which nutrients influence gene expression. Furthermore, advances in molecular and recombinant DNA technology have led to exquisite studies in the field of genetics and the recognition in a much more specific way, through DNA sequencing, of how unique each one of us is, and the extent to which genetic variation occurs in human beings. The importance of the effects of genetic variation has been extensively studied and applied by pharmacologists in drug development and evaluation of drug metabolism and adverse reactions to drugs.^{15–19} In the past two decades physicians, geneticists, and nutritionists began to study the effects of genetic variation, and gene–nutrient interactions in the management of chronic diseases.^{1,2,20}

Data from around the world indicate that the incidence and prevalence of chronic diseases vary among individuals, families and nations. Genetic predisposition, environmental factors, and quality of care all contribute to these variations.^{1,2,5,7,13,20–25} Advances in genetics and molecular biology indicate that susceptibility to chronic diseases such as coronary artery disease,²⁶ hypertension,²⁷ diabetes,²⁸ obesity,²⁹ osteoporosis,³⁰ alcoholism³¹ and cancer^{32–40} etc. to a great extent is genetically determined. Because of genetic variation not everybody is susceptible to chronic diseases to the same degree.^{3,41,42}

Genetic variation, dietary cholesterol and plasma cholesterol levels

It has been known for at least 20 years that the response of plasma cholesterol concentration to cholesterol feeding is

Table 1. Risks for common polygenic diseases of adults

Disorder in proband	Risk for first-degree relatives %
Coronary heart disease	8 for male relatives 3 for female relatives
Diabetes mellitus	5–10
Epilepsy	5–10
Hypertension	10
Thyroid disease	10
Psoriasis	10–15
Manic depressive psychosis	10–15
Schizophrenia	15

Modified from Scott.⁵

heterogeneous, although the mechanisms only recently are being understood.^{43–50}

In certain situations the response to diet appears to be determined by the genetic variant of apolipoprotein, as for example is the case with apolipoprotein E (Apo E). On a low-fat/high-cholesterol diet individuals with Apo E4/4 phenotype respond with an increase in serum cholesterol whereas those with Apo E2/2, Apo E3/2, do not show an increase. On a low-fat/low-cholesterol diet all variants show a decrease in serum cholesterol. Thus, serum cholesterol response to dietary cholesterol is phenotype dependent.⁵¹ The interaction between lipoprotein responsiveness to dietary manipulation and Apo E phenotype has been the subject of several investigations.⁵² A recent meta-analysis study supports the concept that the Apo E4 allele is associated with an increased low-density lipoprotein (LDL) cholesterol response to dietary manipulation.⁵³ On a low-fat/low-cholesterol diet the magnitude of LDL cholesterol lowering is twice as great in male as in female subjects. The lowering of LDL cholesterol in Apo E3/4 male subjects was 23% which was significantly greater than that observed in Apo E3/3 (14%) or Apo E3/2 (13%), suggesting that male subjects with the Apo E3/4 are more responsive to diets restricted in saturated fat and cholesterol than Apo E3/3 male subjects.⁵³

Apo E4 is associated with hypercholesterolemia, whereas the Apo E2 protects against high cholesterol levels. However, in the presence of obesity, hypothyroidism, and diabetes, the variant form of Apo E2 is associated with the development of type III hyperlipoproteinemia and the accumulation of chylomicron and very-low-density lipoprotein (VLDL) remnants in the plasma.⁵⁴ Only one person in 50 with the Apo E2 variant develops hypertriglyceridemia. Because triglyceride removal is genetically determined, increase in either energy intake, *trans* fatty acid intake, or carbohydrate intake (particularly in women) leads to hypertriglyceridemia.

Additional studies show that women of the Apo E3/2 phenotype stand to benefit the least from a high polyunsaturated:saturated (P:S) diet because of reduction in the more 'protective' high-density lipoprotein (HDL) cholesterol, whereas men of the Apo E4/3 phenotype showed the greatest improvement in the LDL:HDL ratio. Therefore, a general recommendation to increase the polyunsaturated content of the diet to decrease plasma cholesterol level and the risk for coronary artery disease is not appropriate for women with the Apo E3/2 phenotype.⁵⁵

Oat bran has been shown to decrease serum cholesterol levels in some studies but not in others. Recently it was shown that only subjects with Apo E3/3 phenotype had a hypocholesterolemic response to oat bran at 4 weeks, but no change was noted in individuals with the Apo E4/4 or E4/3 type.⁵⁶ Thus, specific genetic information is needed to define the optimal diet for an individual. General recommendations usually lead to inconclusive studies or show lack of benefit.

The variant Apo A-IV-1/2 decreases the response of the plasma cholesterol concentration to dietary cholesterol.⁵⁷ In the USA approximately one person in seven is heterozygote

(in other words, carries the Apo A-IV-1/2 allele). The homozygote state is Apo A-IV-1/1. Increasing dietary cholesterol from 200 to 1100 mg/day by the addition of four eggs/day, increased the total cholesterol to 22 mg/dL in the Apo A-IV-1/1 and only to 6 mg/dL in the Apo A-IV-1/2 group. The mean plasma LDL cholesterol increased to 19 mg/dL in the Apo A-IV-1/1 group and only 1 mg/dL in the Apo A-IV-1/2 group. Neither group had any changes in the plasma triglycerides or HDL cholesterol concentration. These results clearly show the effects of genetic variation on the response to dietary cholesterol.

Recent studies employ comparative sequence analysis to define the function of genetic variants. Comparison of genomic DNA sequences from human and mouse revealed a new *APOAV* gene located proximal to the well-characterized *APOA1/CIII/AIV* gene cluster on human chromosome 11q23.⁵⁸ A decrease in plasma triglyceride concentrations to one-third of these in the control mice occurred in the mice expressing a human *APOAV* transgene. Conversely, the knockout mice lacking Apoav had four times as much plasma triglycerides as the controls. In two independent population studies SNP across the *APOAV* locus were found to be significantly associated with plasma triglycerides. Specifically, triglyceride levels were 20–30% higher in individuals having one minor allele compared with individuals homozygous for the major allele. Further studies support the existence of a common haplotype in the *APOAV* region influencing plasma triglyceride levels. Studies involving comparison of human and mouse sequences illustrate the power of comparative sequence analysis to prioritize potential functional regions of the genome. Furthermore:⁵⁸

These results suggest the possible use of *APOAV* polymorphisms as prognostic indicators for hypertriglyceridemia susceptibility and the focus of *APOAV* modulation as a potential strategy to reduce the known cardiovascular disease risk factor.

These findings indicate that *APOAV* is an important determinant of plasma triglyceride levels, a major risk factor for coronary artery disease. The study also reveals another gene variant (*APOAV*), the presence of which protects or decreases the risk for coronary artery disease.

Genetic variation, dietary sodium and the response of blood pressure

Essential hypertension is a common disease. Association between parental blood pressure and a high tracking profile in their children has been confirmed.⁵⁹ Genetic, nutritional and other environmental factors (obesity, sodium, chloride, alcohol, low potassium, low calcium, low omega-3 fatty acid intake, stress, physical inactivity etc.) interact in the development of hypertension.⁵⁹ Variations in blood pressure are due to combined effects of many genes. As a result, different individuals, even within the same family, may be hypertensive due to different combinations of genes. Patients with low plasma renin respond to salt restriction. Genetic differences most likely are responsible for salt sensitivity. Only

half of patients with essential hypertension are salt sensitive. Therefore, a general recommendation to reduce salt intake is not appropriate.

Genetic analyses in human populations support an important role for the renin–angiotensin system in the hypertensive phenotype.⁶⁰ Angiotensin II regulates blood pressure and salt retention. Molecular variants of the renin substrate angiotensinogen have been found to cause an inherited predisposition to essential hypertension. Individuals with certain angiotensinogen gene (AGT) variants associated with hypertension had significant differences in plasma concentration of angiotensinogen.

The angiotensinogen gene has been implicated in the development of hypertension and increased blood pressure. Genetic linkage analysis has shown that the angiotensinogen gene is linked to hypertension in sib pairs in France, England, and Utah.^{60,61} In an attempt to identify a specific mutation that caused increased expression of angiotensinogen levels and increased blood pressure, multiple polymorphisms were examined for association with hypertension.

Recent data indicate that an A for G nucleotide substitution in the promoter region of the angiotensinogen gene-6 nucleotide upstream from the start site of transcription appears to be a functional mutation.^{62,63} The A substitution changes the binding of a nuclear protein, resulting in increased gene transcription compatible with increased angiotensinogen levels. It has been suggested that the angiotensinogen gene in addition to raising blood pressure, also influences the salt sensitivity of the blood pressure.^{63,64} A recent study showed that hypertension incidence differed by genotype over 3 years of follow up.⁶⁵ In the usual care group, systolic and diastolic blood pressure and the incidence of hypertension were higher, but of borderline significance in persons with the AA genotype of the angiotensinogen gene than in those with the GG genotype, whereas the heterozygotes had an intermediate level of blood pressure and a higher incidence of hypertension than persons with the GG genotype. On sodium restriction, individuals with AA and AG lowered their blood pressure whereas those with the GG genotype are salt insensitive. Decreases of diastolic blood pressure at 36 months in the sodium restriction group versus usual care showed a significant trend across all three genotypes ($P = 0.01$) with greater net blood pressure reduction in those with the AA genotype (-2.2 mmHg) than in those with the GG genotype ($+1.1$ mmHg). A similar trend across the three genotypes was observed for systolic blood pressure, but was not significant. Similar blood pressure results were obtained with weight loss. The authors concluded, 'The angiotensinogen genotype may affect blood pressure response to sodium or weight reduction and the development of hypertension'.

In the Dietary Approaches to Stop Hypertension (DASH) study, those who responded by lowering their blood pressure the most had the genotype AA ($-6.93/-3.68$ mmHg) whereas those with the genotype GG responded the least ($-2.80/0.20$ mmHg).⁶⁶ The AA genotype confers excess risk of hypertension and is associated with increased responsiveness to diet.

As mentioned earlier, several complex physiological systems affect blood pressure, including one that is mediated by the 28-amino acid atrial natriuretic peptide (ANP) produced mainly in the cardiac atria.⁶⁷ Pharmacologic doses of ANP lower blood pressure and promote salt excretion. Therefore, efforts have been made to determine whether genetic variants of the ANP system are involved in the aetiology of essential hypertension. Plasma ANP levels are higher in children of two normotensive parents than in children with one hypertensive parent, especially when the children are on a high salt intake. Several polymorphisms have been identified in the human promoter ANP gene. John *et al.* examined the effects of genetically reduced expression of the promoter ANP gene on the blood pressure in mice and on the responses of mice to dietary salt.⁶⁷ Mice were generated with a disruption of the promoter ANP gene. Circulating or actual ANP was not found in the homozygous mutants. Their blood pressure was raised by 8–23 mmHg when fed 0.5% NaCl (standard diet) and 2% NaCl (intermediate) salt diets. On standard salt diets heterozygotes had normal blood pressure and normal amounts of circulating ANP but on 8% NaCl (high salt diets) they became hypertensive with blood pressures elevated by 27 mmHg, indicating that genetically reduced production of ANP can lead to salt-sensitive hypertension. The evidence that ANP modulates the blood pressure response to dietary salt should encourage the search for human genetic variants. Finding such variants may identify patients likely to benefit from reduced salt intake.

Adducin is a protein found in the renal tubule. A polymorphism has been described (Gly 460 Trp) that is associated with changes in blood pressure that may help identify patients who will benefit from sodium restriction or depletion. Hypertensive patients with a 460-Trp allele had a greater decrease in mean arterial blood pressure to both acute and chronic sodium depletion than those homozygous for the wild-type mutation.⁶⁸

The most effective intervention or prevention of hypertension would occur with targeted changes in environmental factors (nutrients, physical activity etc.) matched to an individual's specific genetic susceptibility.

Gene–nutrient interactions and their role in determining nutritional requirements: Folate, a case in point

Nutritional health is dependent on the interaction between the environmental aspects of diet in terms of supply, availability and consumption and the genetically controlled aspects of digestion, absorption, distribution, transformation, storage and excretion by proteins in the form of receptors, carriers, enzymes, hormones etc. (Fig. 1).^{1,2,27,69–72}

The interaction of certain nutrients with genetically determined biochemical and metabolic factors suggests different requirements for individuals, for example familial hypercholesterolemia, familial hypertriglyceridemia, and familial combined hyperlipidemia.^{73,74}

The recommended dietary allowances (RDA) for folate have been substituted by the dietary reference values (RDI)

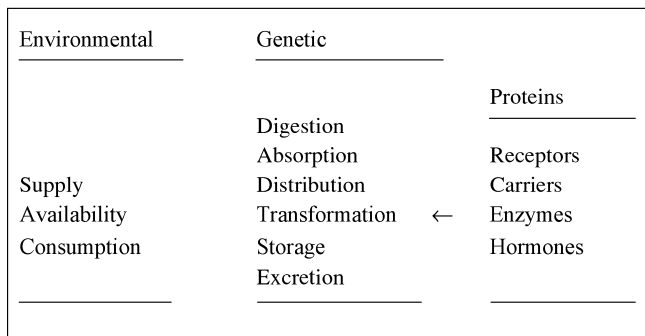


Figure 1. Nutritional health.

which are derived from population-based studies on supposedly normal people. Being designed for the majority of people, they do not cover small groups with special needs such as those with metabolic or genetic abnormalities or disorders.

During the last 10 years a specific thermolabile variant of the folate-related enzyme 5, 10-methylenetetrahydrofolate reductase (MTHFR), which causes partial enzyme deficiency, has been described in 5–15% of normal populations.^{75–78} The mutation 677C→T causes mild hyperhomocysteinemia^{76,79–81} and is positively associated with coronary artery disease^{76,79–81} and an increased risk of neural tube defects.^{82,83} Low serum folate concentrations have been described in some^{80,83,84} but not all⁸¹ studies of people homozygous for the thermolabile variant.

Folate status is an important factor in the development of homocysteinemia. Current dietary reference values for folate may be incorrect for the 5–15% of the people who are homozygous for the thermolabile variant. The established index of tissue-folate stores can be assessed by the red-cell folate concentration.

The importance of genetic variation in establishing dietary reference values is demonstrated by the study of Molloy *et al.*⁸⁵ These investigators studied two groups of healthy women (242 pregnant and 318 non-pregnant). They identified the thermolabile variant of the 5, 10-methylenetetrahydrofolate reductase (C677T) genotype and measured red-cell folate concentrations. The study showed that the red-cell folate was significantly lower in the women with the C677T as was the plasma folate. The pregnant women with the TT variant had even significantly lower folate levels. In this study, 8.3% of the pregnant and 12.9% of the non-pregnant women were positive for C677T. Because 5–15% of the general population are homozygous for C677T, a substantial minority of people in the general population may have increased folate needs. Currently, the dietary reference values for folate, as for other nutrients, are targeted to the general and supposedly normal population, not people with special needs, such as those with genetic or metabolic disorders.

If genetic variants that cause altered nutrient status are common, as this study suggests, there may be no such thing

as a 'normal' population with respect to nutrient requirements, as was assumed when dietary reference values were established.

The role of nutrients in gene expression

There has been an increase in the use of concepts evolved from molecular biology to the study of food components and essential nutrients as factors in the control of gene expression.⁷⁰ In terms of chronic diseases, particularly relevant are the effects of dietary cholesterol and fatty acids on gene expression. Dietary cholesterol exerts a profound inhibitory effect on the transcription of the gene for β -hydroxy- β -methyl-glutaryl (HMG)-CoA reductase.⁸⁶ Dietary PUFA suppress the hepatic mRNA production of fatty acid synthase for lipoproteinemia in adult and weanling rats.⁸⁷ This ability to suppress the abundance of mRNA for lipogenic proteins is dependent on the degree of fatty acid unsaturation. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in the form of fish oils are thus more effective than arachidonic acid (AA).^{72,88–90} Dietary omega-3 fatty acids reduce levels of mRNA for platelet-derived growth factor (PDGF)⁹¹ and for interleukin (IL)-1 β indicating regulation at the transcriptional level.^{92,93} This area of research is expanding very rapidly (Tables 2,3).⁹⁴

Ethnic differences and gene variants

Although man has evolved being able to feed on a variety of foods and to adapt to them, certain genetic adaptations and limitations have occurred in relation to diet. Because there are genetic variations among individuals, however, changes in the dietary patterns impact on a genetically heterogeneous population, although populations with similar evolutionary background have more similar genotypes. Therefore, to be successful, dietary interventions must be based on knowing the frequency of genes the effects of which we are attempting to control or modify.

In north-west Europe the frequency of phenylketonuria (PKU) is approximately 1 in 10 000 live births, but it is much lower in Africans and American Indians.¹⁰² Some rare disorders in most populations are not so rare in some isolated populations. For example, hereditary tyrosinemia occurs in approximately 1 in 1000 live births in a French Canadian group, and hypertyrosinemia is more common in those of Finnish descent.¹⁰²

Hereditary fructose intolerance in Switzerland occurs in 1 in 20 000¹⁰³ and essential pentosuria in people of Jewish origin occurs at 1 in 2500 in some groups.¹⁰²

Populations whose diet did not include wheat, barley, rye or oats manifest gluten sensitivity upon the introduction of those foods in their diet. Celiac disease, triggered by the presence of gluten in the diet, occurs at 1 in 3000 live births in the USA but 1 in 200 in Ireland. Removing gluten from the diet improves the general condition.¹⁰²

Compared to Caucasians (15%), extremely high frequencies of the Apo E4 allele have been found in African and Asian populations such as New Guineans (35%) and Nigerians (30%). Among European populations, northern countries

Table 2. Effects of PUFA on several genes encoding enzyme proteins involved in lipogenesis, glycolysis, and glucose transport

Fatty acids	Hepatic cells		Mature adipocytes	
	lipogenesis FAS, ⁸⁷⁻⁹⁰ S14 ⁸⁷⁻⁹⁰ SCD1 ⁹⁵ SCDII ⁹⁶ ACC, ⁹⁰ ME ⁹⁰	glycolysis G6PD ⁹⁷ GK ⁹⁷ PK ⁹⁸	Glut 4 ⁹⁹	Glut 1 ⁹⁹
LA	↓	†		
LNA	↓	↓		
AA	↓	↓	↓	↑
EPA	↓	↓	↓	↑
DHA	↓↓	↓		

†LA does not suppress PK but suppresses GK and G6PD; ↓, suppress or decrease; ↑, induce or increase.

PUFA, polyunsaturated fatty acids.

Table 3. Effects of PUFA on several genes encoding enzyme proteins involved in inflammation, adhesion molecules, cell growth, early gene expression, β -oxidation, and growth factors

Fatty acid	Cell growth and early gene expression c-fos, Egr-1 ¹⁰⁰	Adhesion molecules VCAM-1 mRNA ^{101**}	Inflammation IL-1b mRNA ^{92,93}	β -oxidation acyl-CoA oxidase mRNA ^{*90}	Growth factors PDGF mRNA ⁹¹
LA				↑	
LNA				↑	
AA	↑	***	↑	↑	↑
EPA	↓	*	↓	↑	↓
DHA	↓	↓	↓	↑↑	↓

*EPA has no effect by itself but enhances the effect of DHA; **monounsaturates also suppress VCAM-1 mRNA, but to a lesser degree than DHA, and induce acyl-CoA oxidase mRNA; ***AA suppresses VCAM-1 mRNA, but to a lesser degree than DHA.

↓, suppress or decrease; ↑, induce or increase.

CoA, coenzyme A; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; IL, interleukin; PDGF, platelet-derived growth factor; PUFA, polyunsaturated fatty acids; VCAM, vascular cell adhesion molecule.

have higher frequencies (Finland 22.7%; Sweden 20.3%) than southern countries (Italy 9.4%), which suggests that Apo E4 may in part account for the differences in cardiovascular disease prevalence in the two European regions. The relationship between LDL cholesterol levels and Apo E genetic variation is not independent of environmental and ethnic factors. The association of the Apo E4 isoform with elevated serum cholesterol levels is greater in populations consuming diets rich in saturated fat and cholesterol than in other populations. Recent data indicate that the higher LDL cholesterol levels observed in subjects carrying the Apo E4 isoform are manifested primarily in the presence of an atherogenic diet characteristic of certain societies, and that the response to saturated fat and cholesterol differs among individuals with different Apo E phenotypes.⁴

Racial differences have been noted in osteoporotic fracture risk. Fracture rates in Africans and Asians are considerably

lower than in White populations despite low dietary intakes of calcium.¹⁰⁴ Alleles of the vitamin D receptor (VDR) gene have been related to bone mineral density, bone turnover, and osteoporotic fracture risk.¹⁰⁵ Age-related changes in bone mass and the influence of calcium intake on bone status have also been related to VDR alleles. Recent studies on the distribution of the VDR alleles show a higher frequency of the b allele in The Gambia and China, where osteoporotic fractures are rare, and a much lower distribution in Cambridge, England. The bb distribution was 37.2% in England (similar to other reports of Northern European ancestry), 76.1% in The Gambia, and 85.3% in China, suggesting that the high frequency of the bb genotype in China and The Gambia may be associated with the low fracture incidence in these countries.¹⁰⁶ Of interest is the fact that the bb distribution in African-Americans in Boston was 43.1%, which is much lower than in The Gambia but higher than in England.¹⁰⁶

The future of genetic nutrition: Nutrigenetics/nutrigenomics

The main use of the human SNP map will be in dissecting the contributions of individual genes to diseases that have a complex, multigene basis. Knowledge of genetic variation already affects patient care to some degree. For example, gene variants lead to tissue and organ incompatibility, affecting the success of transplants. Although the mainstay of medical genetics has been the study of the rare gene variants that lie behind inherited diseases such as PKU and cystic fibrosis, attention has focused on multigenic, multifactorial diseases, such as cardiovascular disease, diabetes, cancer, obesity, osteoporosis etc., and their response to diet.⁴ Phenylketonuria, of course, was the first genetic disease, for which screening programs were developed, that was controlled by diet (a low phenylalanine diet).¹⁰⁷ But variations in genome sequences underlie differences in our susceptibility to, or protection from all kinds of diseases; in the age of onset and sensitivity of illness; and in the ways our bodies respond to treatment with nutrients or drugs. By comparing patterns and frequencies of SNPs in patients and controls, research can identify which SNPs are associated with which diseases.^{108–110} Such research will enhance our understanding of both genetic medicine and genetic nutrition and will expand pharmacogenetics and nutrigenomics/nutrigenetics. This knowledge of our uniqueness will alter all aspects of medicine, nutrition and pharmacotherapy. Because genes and genomes do not act in a vacuum, the environmental factors are equally important in human biology. Genotyping will discover those who, because of genetic variation, require special diets; hence diet will have to be modified to suit the individual or subgroup.

It is estimated that in 5–10 years the pace of discovery of SNP and the developments in high throughput genotyping should lead to the identification of many susceptibility genes for complex disorders. The most precise measurement of this genetic variation is the haplotype, which is the organization of polymorphic variation as it is found on a chromosome. Recently, major government and academic genome researchers have agreed that haplotypes are a powerful tool that can reduce the complexity of genetic information to a practical form. Genaissance Pharmaceuticals has pioneered the industrialization of haplotype discovery, has determined haplotypes for more than 4000 human genes, and is systematically cataloging haplotypes for all the genes in the human genome.¹¹¹ Haplotypes, or HAP™ Markers, can be used in drug discovery to improve the outcome of target validation and drug screening studies and in drug development to improve the design and reliability of clinical trials. The HAP™ Markers can be used to predict the efficacy and safety of new and approved drugs and will serve as the foundation for a new paradigm of personalized medicine: matching patients to the right drug at the right dose via guidance from a database of HAP™ Marker clinical associations. This knowledge might be applied in various clinical settings. To take a hypothetical example, a 45-year-old man with hypertension would have a buccal scrape sample sent

for genetic testing to allow molecular classification of the disease as type I, II, or III. He would then be prescribed a dietary regimen known to be effective in the relevant disease subtype (salt sensitive or not) with or without a specific drug. In a preventative setting a 5-year-old boy whose older sibling has developed asthma might be tested with parental consent and appropriate counseling for asthma susceptibility genes. If the results were positive, he might be prescribed prophylactic drugs to prevent asthma while at the same time he would receive dietary advice to increase the omega-3 fatty acid intake in his diet (e.g. eat more fish) while decreasing the omega-6 fatty acids by avoiding vegetable oils such as corn oil, soybean oil etc. It has been shown that decreasing the omega-6:omega-3 ratio by changing the background diets of persons with autoimmune disorders such as asthma, rheumatoid arthritis, or ulcerative colitis, leads to decreases in IL-1 β and leukotriene B4 (LTB4); improvements of the clinical symptoms; and decreases in the dose of the non-steroidal anti-inflammatory agents.^{112,113} Genotyping will become part of the routine management of an expanding range of human diseases over the next 10 years and nutrigenomics will supplement pharmacogenetics. Knowing who is at risk would be useful if it meant that one could avoid the environmental triggers that convert susceptibility into disease.

How will genetics and nutrigenetics look in the future? Genetics will not remain the exclusive prerogative of regional genetic centers. Instead, every physician will need to use genetic knowledge and combine it with appropriate dietary regimen, type and amount of physical activity, and, if needed, drugs. For common adult-onset conditions such as diabetes and circulatory disorders the interaction between genes and the environment is starting to be understood and there is great interest in the potential for DNA diagnostics.

Potential for novel foods

Already there are products available that are enriched with various nutrients and non-nutrients: 'functional' foods to prevent or treat disease. A major area recently reviewed is the enrichment of products with omega-3 fatty acids.¹¹⁴

Pharmacogenetics is defined as the inherited basis for individual differences in drug response. It is currently dominating pharmaceutical research and development. Nutrigenomics is defined as the inherited basis for individual differences in nutrient (diet) response and it is only beginning to claim its potential. One can visualize the development of beverages and foods either as preventive agents or for the treatment for individuals, families or subgroups predisposed to a particular disease. There is already precedent for this in pediatrics, where ketogenic diets are used for the treatment of patients with intractable epilepsy. Diets balanced in the essential fatty acids are paramount as the background diet for patients with chronic inflammatory diseases, such as arthritis, asthma, ulcerative colitis, lupus etc., as well as in patients with coronary artery disease and hypertension. Specific foods and diets are already used for patients with celiac disease, PKU, and other single gene

diseases. From the marketing standpoint, Fig. 2 shows the flow of information from the identification of the individual based on genetic screening to the marketing of the product. Table 4 shows the expected achievements in genetics in the first quarter of the 21st century.

Global efforts in genetics and biotechnology

There is currently a global effort in structural genomics, which aims to capitalize on the recent success of the genome project. Stevens *et al.* state the following.¹¹⁵

Substantial new investments in structural genomics in the past 2 years indicate the high level of support for these international efforts. Already, enormous progress has been made on high-throughput methodologies and technologies that will speed up macromolecular structure determinations. Recent international meetings have resulted in the formation of an International Structural Genomics Organization to formulate policy and foster cooperation between the public and private efforts.

In their paper, Singer and Daar propose a five-part strategy, including research, capacity strengthening, consensus building, public engagement, and an investment fund.¹¹⁶ It is

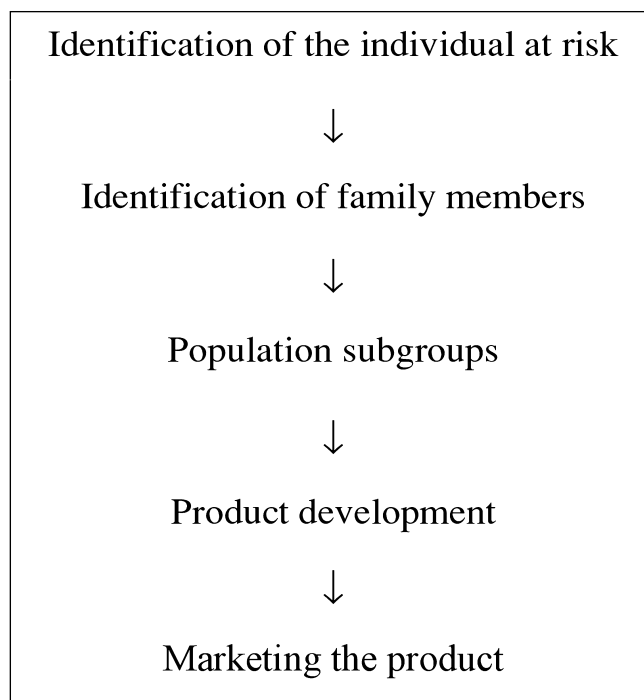


Figure 2. Flow of information from genetic screening to marketing of the product.

essential that genome-related biotechnology can be harnessed to improve global health equity by preventing a health genomics divide from developing. There are already some early and growing examples of genome-related biotechnology being applied successfully to health problems in developing countries, such as the use of polymerase chain reaction techniques for the diagnosis of leishmaniasis and dengue fever in some Latin American countries. Cuba has developed meningitis B vaccine. In fact, biotechnology now ranks third, behind only sugar and tourism among Cuban industries. Brazil has its own genomics and biotechnology industry. Clinical trials have begun in Nairobi and Oxford of an AIDS vaccine (DNA-based) candidate designed specifically for use in Africa. Similarly, hepatitis B and other vaccines are being developed and trials have begun in Africa. India has an International Centre for Genetic Engineering and Biotechnology in Delhi, and China has developed its biotechnology industries. Finally, the Director-General of the World Health Organization (WHO) has asked WHO's highest scientific body, the Advisory Committee on Health Research, to prepare a special report on genomics and world health by the end of 2001. This report will highlight the importance of genomics for the health of the people in developing countries and prepare WHO to be an advocate for improving the health of the disadvantaged and underprivileged.

The term 'nutrigenetics' was first defined by RO Brennan in 1975 in his book *Nutrigenetics. New Concepts for Relieving Hypoglycemia*.¹¹⁷ It is essential that nutrigenomics will take into consideration at this time the importance of the ethical, legal, economic, scientific and behavioural aspects of genetic screening, as were recommended by the National Academy of Sciences–National Research Council in its 1975 report *Genetic Screening: Programs, Principles and Research*.¹⁰⁷ Although a number of other reports have been published since 1975, this book remains a classic as shown by the following recent quotation.¹¹⁸

This early classic in the field of genetic screening provides an ongoing framework to study the prospects, history, and development of principles, legislation, and program guidelines applicable to genetic testing aims, methodology and education. Ethical aspects are presented from the view of a 'perfect' screener, who would have all relevant facts to provide both error-free testing and effective counseling; possess a strong sense of the thoughts and emotions of those screened; be as free as possible from self-interest and inappropriate emotionalism; and apply principles consistently.

Table 4. Genetics: expectations for the 21st century

First quarter
Identify disease/gene associations for many illnesses and function of genes
Expand nutrigenomics and pharmacogenomics (treatment and prevention)
Responsiveness to interventions (nutrients, drugs) will be predicted, because variation in the responses is often attributable to the genetic profile of the individual
Individualize prescriptions, diets, and lifestyle modifications and/or drug treatment
Develop gene-based designer diets for coronary artery disease, hypertension, diabetes, arthritis, asthma, mental health etc.

The US government has established a commission to safeguard the privacy of the individuals and to avoid discrimination in employment, and health and life insurance; and a bill banning genetic discrimination in insurance policies and in the workplace is expected to pass US Congress and be signed by the President early in 2002. In the UK the insurance companies have agreed to a 5-year ban on using genetic tests.¹¹⁹ Furthermore, the Fogarty International Center of the National Institutes of Health (USA), along with several other agency institutes and WHO, will support an international research training program in human genetics with \$15 million over the next 5 years.¹²⁰ The program aims to enhance the technical capacity in genetic science in developing regions of the world.

Conclusions and recommendations

The new genetics has enormous implications for nutrition research both in the prevention and management of chronic diseases. The new millennium is a remarkable time for medicine and nutrition when the potential for improving human health is unequalled in history. With the unfolding genomic and technological revolution, continuing investments in research offers unprecedented opportunities to understand disease processes, prevent intrinsic and environmental risks to health and develop new approaches to improve the quality of life worldwide. Although the emphasis of new genetics has been on pharmacogenetics, it is the responsibility of the nutrition scientists to expand in parallel the relationship of genetics and nutrition and establish nutrigenomics/nutrigenetics as a major discipline in nutrition in the 21st century.

Scientific institutions and WHO have recognized the importance of the advances in human genetics to health. They have proposed the development of programs to enhance the technical capacity in genetic science in the developing regions of the world, in order to reduce disparities in health status between developed and developing countries through the use of genetic science. In doing so, special consideration should be given to privacy issues and avoidance of discrimination by health insurance companies and employers.

In the future, the focus will shift to prevention. It will be easier, indeed routine, to identify genetic predispositions in family members at risk, and probably those at risk in the population at large. As a consequence, it will be necessary to educate people at risk to the advantages of maintaining healthy lifestyles, avoiding risk, and seeking out preventive therapies. Furthermore, knowledge of genetic susceptibility to disease will help identify those at higher risk for disease, as well as their response to diet. As a result there will be a need for the development of novel foods targeted to individuals, families and subgroups within populations.

There is no single universal approach for what we are calling the 'lifestyle' approach to diseases with genetic predisposition. The approach will have to vary with national dietary patterns and national economy. Therefore, it will be necessary to promote lifestyle patterns that will be compatible with a healthier phenotypic expression of genotypes

evolved under different conditions, which means individualized prescriptions and gene-based designer diets.

The prospect of targeting specific dietary treatment to those predicted to gain the most therapeutic benefit clearly has important clinical and economic consequences, particularly in diseases of high prevalence such as coronary artery disease, hypertension, diabetes, osteoporosis, and possibly cancer.

Because the same genotype may not confer the same risk in all populations, populations should not copy each other's dietary recommendations for the prevention of coronary artery disease, and cancer, or any other disease for that matter.

Universal dietary recommendations have been used in the past by nutritionists who were concerned with undernutrition; but universal dietary recommendations are not appropriate when the problem is one of overnutrition. Individual dietary recommendations taking into consideration genetic predisposition and energy expenditure are in order.

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