Nutrigenetics/Nutrigenomics

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Abstract

All diseases have a genetic predisposition. Genome-wide association studies (GWASs) by large international consortia are discovering genetic variants that contribute to complex diseases. However, nutrient information is missing, which is essential for the development of dietary advice for prevention and management of disease. Nutrigenetics/nutrigenomics studies provide data on mechanisms of nutrient and gene interactions in health and disease needed for personalized nutrition. A process will be needed to define when gene-nutrient-disease associations are ready to be evaluated as potential tools to improve public health.

INTRODUCTION

The interaction of genetics and environment, nature and nurture, is the foundation for all health and disease (78, 80, 81). Genes define susceptibility to a disease or condition, and environmental factors such as diet and exercise determine who among the susceptibles will develop the disease or condition (**Figure 1**).

Nutrition is an environmental factor of major importance. Methodological advances in molecular biology and genetics have facilitated the study of inherited disease at the DNA level and of nutrients at the molecular level. This research has led to (*a*) the development of concepts and research on genetic variation and dietary response, known as nutrigenetics (e.g., individuals responding differently to the same diet by attaining different levels of serum cholesterol and blood pressure because of genetic variation), and (*b*) studies on the evolutionary aspects of diet and the role of nutrients in gene expression, known as nutrigenomics [e.g., polyunsaturated fatty acids (PUFA) suppress fatty acid synthase (mRNA) gene expression]. The term nutrigenetics was introduced by Brennan in 1975 in "Nutrigenetics: New Concepts for Relieving Hypoglycemia" (7). Nutrigenetics/nutrigenomics could provide a framework for development of genotype-dependent novel foods for health promotion and for prevention and management of chronic diseases. National general dietary guidelines have been issued for the prevention of chronic diseases without considering effects of genetic variation on dietary responses, despite such evidence (59, 98).

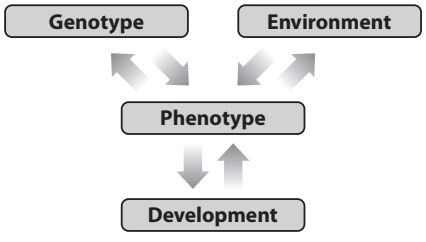

Figure 1

Relationships between genes, environment, and development are dynamic (78).

This article is organized in four sections: (*a*) definition of heritability, (*b*) major examples of nutrigenetics, (*c*) nutrigenomics evidence of dietary manipulations of gene expression, and (*d*) future prospects and recommendations. Critical concepts are highlighted through examples that are relevant to public health.

HERITABILITY, THE PROPORTION OF VARIABILITY IN RISK DUE TO GENETIC FACTORS

Coronary heart disease (CHD), high blood pressure, diabetes, cancers, and other chronic diseases tend to aggregate in families; risk among relatives is higher than in the general population (70). Families share both genes and environment; similarity may result from either. In families with CHD onset before age 46, heritability was estimated to be 92%–100%; within families with older index cases, the heritability ranges from 15% to 30%. Heritability is the proportion of the total variance that can be explained by genes and gene-environment interactions (85). For example, 50% of the variance in plasma cholesterol concentration is genetically determined (62, 94); 30%–60% for blood pressure (60); 15% in the United Kingdom (37) to 50% in Sweden (34) for fibrinogen, an independent risk factor for CHD; and 75% in Australia for bone density (61). Calculations of heritability are tied to the specific population and environment studied and vary if populations differ in the prevalence of the relevant genetic alleles. Population subgroups may need to have specific dietary recommendations for the prevention of CHD or certain cancers or other diseases.

NUTRIGENETICS: GENETIC VARIATION AND DIETARY RESPONSE

A fundamental aspect of the genetic approach to disease is an appreciation of human variation: its nature and extent, origin and maintenance, distribution in families and populations,

interactions with environment, especially diet and exercise, and consequences for normal development and homeostasis (5, 6, 78). Some of the earliest studies of human biochemical genetics showed considerable variability within and between populations, which is highly relevant for nutrition (78). Variation in nutritional requirements and interaction of certain nutrients with genetically determined biochemical and metabolic factors suggest different requirements for individuals (59, 98). This variation (like sex differences) is inborn and needs to be differentiated from variations caused by the life cycle (growth, pregnancy, and old age). 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 (63). Genetic variation and gene-nutrient interactions are also important in drug metabolism and adverse reactions to drugs.

Phenylketonuria (PKU) was the first "inborn error of metabolism" caused by a single-gene defect that responded to dietary treatment, employing a low-phenylalanine-containing diet for nutrigenetic management. There are ~6000 single-gene disorders, of which 2000 have been identified (28, 55). Chronic diseases such as CHD, hypertension, diabetes, cancer, and obesity are multigenetic and multifactorial. The same phenotype may be due to different heterogeneous genes. In polygenic diseases, the interaction between genes and environmental factors is responsible for inducing the phenotype. Single-gene disorders tend to be relatively rare, with incidence less than 1 in 1000 births or persons; generally they are under negative selective pressure.

During the past few years, genome-wide association studies (GWASs) have revealed genomic variants (alleles) predisposing to diabetes (82), prostate cancer (1), lupus (32), age-related macular degeneration (48), Crohn's disease (99), and other diseases. For CHD, a major locus has been identified on chromosome 9p21 (56). The locus is heterozygous in 50% of Caucasians with an increased risk of 15%–20% and homozygous in 25% of Caucasians with an increased risk of 30%–40%. This variation has been confirmed in Icelandic, British, German, and Central European populations for 60,000 Caucasians and in Korean, Japanese, Chinese, and East Asians. Preliminary evidence suggests 9p21 is not a risk factor for African Americans. The 9p21 variant is a novel risk factor for CHD and cerebral vascular disease, independent of known risk factors such as diabetes, hypertension, cholesterol, and obesity. This information implies a new mechanism for CHD with respect to vascular pathology, perhaps separate from the lipid hypothesis (66).

Gene–Nutrient Interactions and Their Role in Determining Nutritional Requirements: Folate

Nutritional health is dependent on the interaction between the environmental aspects of supply, bioavailability, consumption, and coingestion of dietary components and the genetically controlled aspects of digestion, absorption, distribution, transformation, storage, and excretion by proteins in the form of receptors, carriers, enzymes, and hormones (4, 10, 68, 95). Such interactions lead to different requirements for individuals, for example, with familial hypercholesterolemia, familial hypertriglyceridemia, and familial combined hyperlipidemia (31).

A specific thermolabile variant of the folate-related enzyme 5, 10-methylenetetrahydrofolate reductase (MTHFR) has been described in 5%–15% of normal populations (27, 45, 47). The mutation 677C→T, which causes partial enzyme deficiency, leads to mild hyperhomocysteinemia (23, 27, 44, 49) and is positively associated with CHD and an increased risk of neural tube defects (90, 93). Low serum folate concentrations have been described in some (23, 46, 90) but not all (49) studies of people who are homozygous for the thermolabile variant. The established index of tissue folate stores can be assessed by the red-cell folate concentration. Molloy et al. (59) identified the thermolabile variant of MTHFR (C677T

genotype) and measured red-cell folate concentrations in 242 pregnant and 318 nonpregnant healthy women. Red-cell folate and plasma folate were significantly lower in the nonpregnant women and even lower in the pregnant women with the TT variant. 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.

Genetic Variation, Dietary Cholesterol, and Plasma Cholesterol Levels

For more than 20 years, investigators have known that the response of plasma cholesterol concentration to cholesterol feeding is highly variable in populations (30, 58, 63, 71, 72, 74). On a low-fat/high-cholesterol diet individuals with Apolipoprotein *E4/4* genotype respond with an increase in serum cholesterol, whereas those with Apo *E2/2* or 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 genotype-dependent (53, 57). The lowering of low-density lipoprotein (LDL) cholesterol in Apo *E3/4* male subjects was 23%, compared with 14% in Apo *E3/3* and 13% in Apo *E3/2* on a low-fat/low-cholesterol diet. Furthermore, the magnitude of LDL cholesterol lowering was twice as great in males as in females (53).

Apo *E4* is associated with hypercholesterolemia, whereas Apo *E2* protects against high cholesterol levels. However, in the presence of obesity, hypothyroidism, or diabetes, 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 1 person in 50 with the Apo *E2* variant develops hypertriglyceridemia in the presence of obesity, hypothyroidism, or diabetes. Because triglyceride removal is genetically determined, an increase in 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 polyunsaturate:saturate (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 CHD is not appropriate for women with the Apo *E3/2* phenotype (18). Some studies, but not others, have shown that oat bran decreases serum cholesterol levels. Only individuals with the Apo *E3/3* phenotype had a hypocholesterolemic response to oat bran at four weeks; no change was noted in individuals with the Apo *E4/4* or *4/3* type (88).

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.

Genetic Variants in the 5-Lipoxygenase: the Role of Omega-6 and Omega-3 Fatty Acids in Coronary Heart Disease

Omega-6 fatty acids, linoleic acid (LA), and arachidonic acid (AA) account for the majority of polyunsaturated fatty acids (PUFA) in the U.S. food supply (77). They are the predominant PUFA in all diets, especially Western diets. The omega-3 fatty acids include alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Their blood levels are determined by dietary intake and by genetic variants in the FADS1 and FADS2 gene cluster (69). Competition between the omega-6 and omega-3 fatty acids occurs in prostaglandin formation. Eicosapentaenoic acid (EPA), an omega-3 fatty acid, competes with AA, an omega-6 fatty acid, for prostaglandin and leukotriene synthesis at the cyclooxygenase and lipoxygenase levels (**Figure 2**). Proinflammatory eicosanoids of AA metabolism

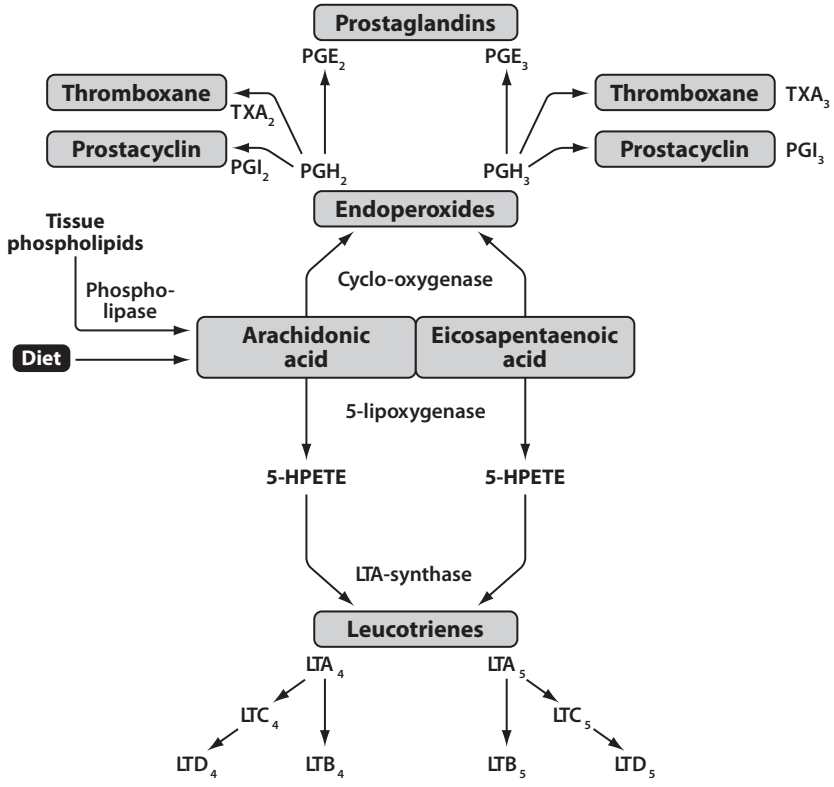

Figure 2

Oxidative metabolism of arachidonic acid and eicosapentaenoic acid by the cyclooxygenase and 5-lipoxygenase pathways. 5-HPETE denotes 5-hydroperoxyeicosatetranoic acid and 5-HPEPE denotes 5-hydroxyeicosapentaenoic acid.

are released from membrane phospholipids in the course of inflammatory activation. EPA is released to compete with AA for enzymatic metabolism inducing the production of less inflammatory and chemotactic derivatives.

Because atherosclerosis involves arterial inflammation, Dwyer et al. (22) hypothesized that a polymorphism in the 5-lipoxygenase gene promoter could relate to atherosclerosis in humans and that this effect could interact with the dietary intake of competing 5-lipoxygenase substrates. The study consisted of 470 randomly sampled, healthy, middle-aged women and men from the Los Angeles Atherosclerosis study. The investigators determined 5-lipoxygenase (5-LO) genotypes, carotid-artery intima-media thickness, markers of inflammation, C-reactive protein (CRP), IL-6 (interleukin-6), dietary AA, EPA, DHA, LA, and ALA with the use of 6 24-hour recalls of food intake. The results showed that 5-LO variant genotypes were found in 6% of the cohort. Mean intima-media thickness adjusted for age, sex, height, and racial or ethnic group was increased by 80 ± 19 μm among the carriers of two variant alleles as compared with carriers of two copies of the common (wild-type) allele. In multivariate analysis, the increase in intima-media thickness among carriers of two variant alleles (62 μm, $p < 0.001$) was similar in this cohort to that associated with diabetes (64 μm, $p < 0.001$), the strongest common cardiovascular risk factor. Increased dietary AA significantly enhanced the apparent atherogenic effect of genotype, whereas increased dietary intake of omega-3 fatty acids

EPA and DHA blunted this effect. Furthermore, the plasma level of CRP with two variant alleles was increased by a factor of two, compared with that among carriers of the common allele. Thus, genetic variation of 5-LO identifies a subpopulation with increased risk for atherosclerosis. The diet-gene interaction further suggests that dietary omega-6 fatty acids promote, whereas marine omega-3 fatty acids EPA and DHA inhibit, leukotriene-mediated inflammation, which leads to atherosclerosis in this subpopulation.

The prevalence of variant genotypes differed across racial and ethnic groups, with much higher prevalence among blacks (24.0%), Asians or Pacific Islanders (19.4%), and other racial or ethnic groups (18.2%) than among Hispanic subjects (3.6%) and non-Hispanic whites (3.1%). The study constitutes evidence that genetic variation in an inflammatory pathway—in this case the leukotriene pathway—can trigger atherogenesis in humans. These findings could lead to new dietary and targeted molecular approaches for the prevention and treatment of cardiovascular disease according to genotype, particularly in the populations of non-European descent.

Genetic Variants in the 5-Lipoxygenase: Omega-6 Fatty Acids and Breast Cancer

A number of epidemiologic studies and animal experiments suggest that omega-6 fatty acids increase the risk of certain cancers, whereas omega-3s decrease these risks. However, not all studies have yielded consistent results. The 5-lipoxygenase pathway has been implicated in carcinogenesis and tumor progression in lung (3), colon (83, 97), prostate (29, 84), kidney (24), and bladder (35) cancers. Earlier epidemiologic studies on dietary fat intake and breast cancer did not find positive association between omega-6 and breast cancer risk. Those studies, however, did not account for genetic predisposition related to omega-6 fatty acid metabolism. Wang et al. (92) determined genetic variants in the 5-lipoxygenase gene (*ALOX5)* and 5-lipoxygenase-activating protein gene (*ALOX5AP*) in combination with dietary LA intake in a population-based multiethnic case control study on breast cancer in Latin, African American, and white women in the San Francisco area (**Figure 2**). The authors did not find significant main effects of *ALOX5* and *ALOX5AP* genotypes on breast cancer risk that were consistent across race or ethnicity. However, there was a significant interaction between the *ALOX5AP*–4900 A>G polymorphisms and dietary LA intake ($p = 0.03$). Among women consuming a diet high in LA (top quartile of intake >17.4 g/d), carrying the AA genotype was associated with higher breast cancer risk (age- and race-adjusted odds ratio 1.8; 95% confidence interval 1.2–2.9), compared with carrying genotype AG or GG. Among women consuming ≤17.4 g/d of LA, *ALOX5AP*–4900 genotype was not associated with breast cancer risk. These findings indicate that studies on dietary fat intake and cancer should consider type of fat and genetic variant predisposition. Furthermore, in the United States, 17.4 g/d is the intake that a significant portion of the population ingests. A recent study showed that the mean LA intake in the mean upper one-third of the NHANES (National Health and Nutrition Examination Survey I Epidemiologic Follow-Up Study 1971–1982 data) is 19.3 g/d in men and 13.4 g/d in women (96). It is unfortunate that the American Heart Association recommended a LA intake up to 10% of calories, which is 22 g/d on a 2000 cal/d diet, thus putting a significant number of women at risk.

Genetic Variants of COX-2 and the Protective Effect of Long-Chain Omega-3 Fatty Acids in Prostate Cancer

Prostate cancer is the most common cancer in men. Increasing evidence points to chronic inflammation as one of the factors leading to this cancer. Inflammation may result from bacterial or viral infections, intraprostatic urine reflux, or diet. Dietary components that are potent anti-inflammatory agents are the omega-3

polyunsaturated fatty acids. Studies have shown that variants of the *COX-2* gene modify prostate inflammation through the COX-2 enzymatic pathway (**Figure 2**). COX-2 is a key enzyme in fatty acid metabolism and inflammation. In a case-control study of 466 men diagnosed with aggressive prostate cancer and 478 age- and ethnicity-matched controls, Fradet et al. (25) genotyped nine *COX-2* tag SNPs. Dietary history was assessed semiquantitatively with a food-frequency questionnaire. Increasing omega-3 intake was associated with a decreased risk of aggressive prostate cancer, which was even stronger among men with genetic variants rs 4648310 (+ 8897 A/G) flanking the 3′-region of *COX-2*. The patients with the lowest intake of omega-3s and the genetic variant had the most aggressive tumors, whereas the omega-3 PUFAs were protective. In this gene by diet (omega-3) interaction, the main dietary effect was modified by the genetic variant: men with the variant genotype AG or GG and low intake of omega-3s had much higher risk than did men with the variant genotype and high intake of omega-3s. Higher intake of dark fish was associated with significantly decreased risk of prostate cancer. Men who ate dark fish one to three times per month had a 36% lower risk of prostate cancer, in comparison with men who never ate dark fish (OR, 0.64; 95% CI, 0.48–0.86). Furthermore, those who ate dark fish more than once per week had an even larger reduction in risk compared with those who never ate dark fish (OR, 0.43; 95% CI, 0.29–0.63).

A study of Swedish men (36) found that frequent consumption of fatty fish (rich in omega-3s) was inversely associated with prostate cancer risk only in men carrying the variant allele rs 5275 (+6364 A>G) SNP in *COX-2*.

Dietary factors and genetic interactions could explain the discrepancies noted in association studies. Increasing omega-3 intake and decreasing omega-6 intake, leading to a balanced omega-6/omega-3 ratio, as it was during evolution when our genes were programmed to respond to a balanced ratio, is the recommendation most appropriate to improve public health (77).

Genetic Variation, Dietary Sodium, and the Response of Blood Pressure

Essential hypertension is a common disorder. Association between parental blood pressure and a high tracking profile in their children has been confirmed (95). Genetic, nutritional, and other environmental factors (obesity, sodium, chloride, alcohol, low potassium, low calcium, low omega-3 fatty acid intake, stress, physical inactivity) interact in the development of hypertension. 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 owing to different combinations of genes.

Angiotensin II regulates blood pressure and salt retention (41). Individuals with certain angiotensinogen gene (*AGT*) variants associated with hypertension have significant differences in plasma concentration of angiotensinogen depending on the genetic variant. Genetic linkage analysis has shown that the angiotensinogen gene is linked to hypertension in sib pairs in France, England, and Utah (11, 41). 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 (39, 40). The A substitution changes the binding of a nuclear protein, resulting in increased gene transcription compatible with increased angiotensinogen levels, which raise blood pressure and influence the salt sensitivity of the blood pressure (33, 39). After more than three years of follow-up in the usual care group, systolic and diastolic blood pressure and the incidence of hypertension were higher, but the levels were of borderline significance in persons with the *AA* genotype of the angiotensinogen gene compared with those with the *GG* genotype, whereas the heterozygotes had an intermediate level of blood pressure and a higher incidence of hypertension than did persons with the *GG* genotype (38). On sodium restriction, individuals with *AA* and *AG* lowered their blood pressure, whereas those with the *GG* genotype were salt insensitive. Therefore, a recommendation

to lower salt intake in those with the *GG* genotype would be ineffective and unnecessary. 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 mm Hg) than in those with the *GG* genotype (+1.1 mm Hg). 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" (86). 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 mm Hg), whereas those with the genotype *GG* responded the least (−2.80/0.20 mm Hg) (86). The *AA* genotype confers excess risk of hypertension and is associated with increased responsiveness to diet.

Adducin is a protein found in the renal tubule. One polymorphism (Gly 460 Trp) 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 did those homozygous for the wild-type mutation (20).

A recent GWAS of blood pressure and hypertension (52) identified 13 SNPs for systolic blood pressure, 20 for diastolic blood pressure, and 10 for hypertension at $P < 4 \times 10^{-7}$. However, as in other GWA studies, so far interactions with nutrients or exercise were not studied. Furthermore, none of the genes identified as having common variants is part of a known system that regulates blood pressure. The genes identified are not the ones targeted by current prescription drugs to control hypertension. If new mechanisms emerge from these studies, the findings could change our understanding of the biology of blood pressure control and offer new targets for therapy or prevention. 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.

NUTRIGENOMICS: THE EFFECTS OF NUTRIENTS ON GENE EXPRESSION

Omega-6 and Omega-3 Fatty Acids

Over the past 25 years there has been an increase in the application of concepts from molecular biology to studies of food components and essential nutrients as factors in the control of gene expression (68). In terms of chronic diseases, particularly relevant are the effects of dietary cholesterol and fatty acids. Dietary cholesterol exerts a profound inhibitory effect on the transcription of the gene for β-hydroxy-β-methyl-glutaryl (HMG)-CoA reductase (64). Dietary PUFAs suppress the hepatic mRNA production of fatty acid synthase for lipoproteinemia in adult and weanling rats (14). This ability to suppress the abundance of mRNA for lipogenic proteins is dependent on the degree of fatty acid unsaturation. EPA and DHA in the form of fish oils are thus more effective than AA (13, 15, 16). Dietary omega-3 fatty acids reduce levels of mRNA of platelet-derived growth factor (PDGF) (43) and of IL-1β, indicating regulation at the transcriptional level (67, 73, 87). This area of research is expanding very rapidly.

Carbohydrates

The metabolic syndrome, characterized by central obesity, hypertension, dyslipidemia, hyperinsulinemia, insulin resistance, and hyperglycemia, predisposes to cardiovascular disease and type II diabetes (50, 51, 65). Diet, physical activity, and genetic predisposition appear to interact and influence both its development and its progression. The question here is how and whether these interactions influence gene

expression. Kallio et al. (42) tested two different carbohydrate modifications—a rye pasta diet characterized by a low postprandial insulin response and an oat-wheat-potato diet characterized by a high postprandial insulin response—on gene expression in subcutaneous adipose tissue in persons with metabolic syndrome. The authors performed adipose tissue biopsies, oral glucose-tolerance tests, and other biochemical measurements in 47 subjects (24 men and 23 women with a mean age of 55 $\pm$ 6 years) with the features of the metabolic syndrome in a parallel study design. Body mass index (BMI) was 32.1 $\pm$ 3.8, with 2-h plasma glucose concentration of 8.0 $\pm$ 2.3 mmol/L. The response in the rye-plasma group was downregulation of 71 genes, including genes linked to insulin signaling and apoptosis, whereas the 12-week oat-wheat-potato diet upregulated 62 genes related to stress, cytokine-chemokine-mediated immunity and the interleukin pathway. There was no change in weight, but the insulinogenic index improved after the rye-pasta diet ($p = 0.004$) and not after the oat-wheat-potato diet, indicating that dietary modification modulates gene expression and metabolism in patients with the metabolic syndrome, even in the absence of weight loss.

Calorie Restriction

Crujeiras et al. (19) used peripheral blood mononuclear cells to evaluate gene expression in Caucasian obese men on an eight-week low-calorie diet (LCD). All subjects lost at least 5% of body weight as a result of the hypocaloric diet. The microarray comparison before and after the nutritional intervention resulted in 385 differentially expressed genes, with 158 genes overexpressed or upregulated and 227 genes downregulated after the LCD. Genes encoding factors involved in nucleotide, DNA, and chromatin metabolism, as well as in cellular biosynthesis and regulation of metabolic processes and protein and lipid pathways, were mostly upregulated ($p \leq 0.05$), whereas those related to signal transduction, cell communication, transport, immune response, and carbohydrate metabolism were mostly downregulated. Of interest, IL-8 was associated with a higher fat mass decrease after the LCD. A decrease in gene expression occurred in some specific oxidative stress and inflammation genes and was related to body weight loss.

The genes related to signal transduction, cell-cell signaling, immune response, and insulin sensitivity, such as TNF-alpha/NF-kB signal cascade pathway, were mostly downregulated by caloric restriction, whereas the protein-DNA assembly complex and biosynthetic and metabolic regulatory processes were upregulated. Similar results have been reported in adipose tissue after 28-day very LCDs (17). It is possible that not only weight loss but also the negative energy balance could have influenced the regulation of genes involved in oxidative stress and inflammation. Caloric restriction by itself has been suggested to regulate adipose tissue gene expression independently of fat mass loss (91).

Dahlman et al. (21) studied changes in adipose tissue gene expression with energy-restricted diets in 40 obese women randomly assigned to either moderate fat/moderate carbohydrate diet or a low-fat/high-carbohydrate hypoenergetic (−600 kcal/d) diet for 10 weeks. Adipose tissue samples were obtained subcutaneously before and after the diet period. High-quality RNA samples were obtained from 23 women at both time points and were hybridized to microarrays containing probes for 8500 human genes. Both diets resulted in weight losses of 7.5% of baseline body weight. A total of 52 genes were significantly upregulated and 44 were downregulated, with no diet-specific effects. Most changes were modest (<25% of baseline), but all genes regulating formation of PUFAs from acetyl-CoA and malonyl-CoA were markedly downregulated (25%–60% decrease) (21). The authors concluded that macronutrients have a secondary role in changes in adipocyte gene expression after energy-restricted diets. The most striking alteration after energy restriction is a coordinated reduction on the expression of genes regulating the production of PUFAs.

Nutrition and Lifestyle

Carter et al. (9) carried out the Gene Expression Modulation by Intervention with Nutrition and Lifestyle (GEMINAL) study, a prospective single-arm pilot clinical intervention study in 30 men with indolent low-risk prostate cancers, defined by strict clinical and pathologic criteria, designed to minimize the risk for metastatic disease through participation in the study. The participants undertook comprehensive lifestyle changes (low-fat, whole foods, plant-based nutrition; stress management techniques; moderate exercise; psychological group support). Prostate needle biopsies were obtained at baseline and three months after lifestyle intervention for mRNA. Microarrays detected 48 upregulated and 453 downregulated transcripts after the intervention. Pathway analysis identified significant modulation of biological processes that have critical roles in tumorigenesis, including protein metabolism and modification, intracellular protein traffic, and protein phosphorylation ($p < 0.05$). Thus, intensive nutrition and lifestyle changes may modulate gene expression in the prostate. This intervention was complex; future studies may differentiate which components or combinations of components produce particular molecular effects. Unfortunately, genetic variation was not investigated in this study.

Exercise, Obesity, and Diabetes

In 2007, Frayling et al. (26), while performing a genome-wide search for type 2 diabetes susceptibility genes, identified a common variant in the FTO gene that predisposes to diabetes through an effect on BMI. The 16% of adults who were homozygous for the FTO risk allele weighed ~3 kg more and had a 1.67-fold increased risk of obesity when compared with those not inheriting the risk allele. This association was found from age 7 years and reflects a specific increase in fat mass. The FTO gene does not appear to influence fetal weight or body weight during infancy. Although the FTO variant (rs9939609) was found to associate with type 2 diabetes, this association was abolished following adjustment for BMI. The association with overweight and obesity was demonstrated in seven white European populations comprising 19,424 adults and 10,172 white European children. The increase in BMI resulted from an overall increase in body fat evaluated by waist circumference and fat mass estimates, including skin folds. Although the function of the FTO gene product and the involved biological pathways are as yet unknown, gene expression profiles show that FTO is expressed in several tissues including brain and muscle (26). This association has been replicated in several additional studies, using data on more than 80,000 adults and children. The statistical power of ($p \approx 1.2 \times 10{:}29$) in the aggregate data is much higher than for any previous candidate-gene association.

Andreasen et al. (2) studied the effect of FTO variation on obesity, type II diabetes, and related quantitative traits in a sample of Danes and found that low physical activity appears to accentuate the effect of FTO rs9939609 on body fat accumulation. In middle-aged individuals, the FTO rs9939609 genotype may be associated with decreased whole-body insulin sensitivity. In homozygous carriers of the FTO A-allele, physical inactivity is associated with a large increase in BMI compared with that in noncarriers and those heterozygous for the A-allele.

Cecil et al. (12) studied the effects of genetic variation in the FTO gene rs9939609 in children. The major effect appears to be on energy intake and preference for foods of high caloric density. The magnitude of the increase in energy intake correlated with the A allele of the SNP is high enough to account for some or all of the differences in adiposity. No effect of genotype at rs9939609 on resting energy expenditure (corrected for body size) was detected, and estimated physical activity actually increased. Excess intake is probably the major mechanism for obesity in children (12).

FUTURE PROSPECTS AND RECOMMENDATIONS

In 2007 the U.S. government established the Genes and Environment Initiative (GEI), which has two main components (**http://wwww.gei.nih.gov**). First, the genetics program is a pipeline for analyzing genetic variation in groups of patients with specific illnesses. Second, the exposure biology program is an environmental technology development program to produce and validate new methods for monitoring environmental exposures that interact with a genetic variation for the development of human diseases. NIEHS is working on an "exposome."

GEI invests in innovative new technologies to measure environmental toxins, dietary intake, and physical activity and to determine an individual's biological response to those influences using new tools of genomics, proteomics, and metabolomics.

How will genetics and nutrigenetics/nutrigenomics look in the future? Genetics will not remain the exclusive prerogative of regional genetic testing and counseling centers. Instead, every physician will need to learn to evaluate and explain genetic knowledge about their patients and combine it with an appropriate dietary regimen, the type and amount of physical activity, and, if needed, pharmaceuticals. Public health professionals will utilize genetic information to identify population subgroups with significantly different responses to diet, infection, and environmental exposures.

Genotyping will become part of the routine management of an expanding range of human diseases over the next 5–10 years, and nutrigenetics 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. New knowledge will be added to the PharmacoGenomics Knowledgebase (PharmGKB; **http://www.pharmGKB.org**).

Nutrigenetics 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. A precedent in pediatrics is the use of ketogenic diets in treatment of patients with intractable epilepsy. Specific foods and diets are routinely used for patients with celiac disease, as well as PKU and other inborn errors of metabolism. Diets balanced in the essential fatty acids (omega-6 and omega-3) are paramount as the background diet for patients with chronic inflammatory diseases, such as arthritis, asthma, ulcerative colitis, lupus, and atherosclerotic CHD (8, 79). There is potential for novel foods, known as functional foods, to prevent or treat disease. One example is the enrichment of products with omega-3 fatty acids (75). From the marketing standpoint, **Figure 3** shows the flow of information from the identification of the individual, based on genetic screening, to the marketing of the product.

Looking ahead 15–25 years in twenty-first century, we can project the following achievements in nutrigenetics and nutrigenomics.

1. Gene/nutrient associations will be discovered for many illnesses.
2. Nutrigenomics and pharmacogenomics will be integrated and applied in the

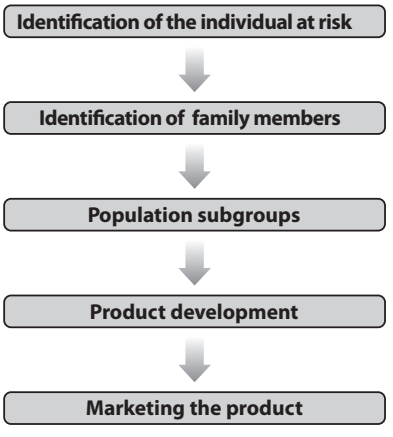

Figure 3

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

therapy and prevention of many diseases, with individualized prescriptions and lifestyle modifications.

3. Populations will be stratified into subgroups according to their genotypes and dietary histories to predict responsiveness to appropriate nutrient and drug interventions.
4. Gene-based designer diets will be developed for coronary artery disease, diabetes, high blood pressure, arthritis, asthma, mental illnesses, and other disorders.
5. Nutrigenomic studies involving calorie restriction, specific carbohydrate and fat features, and exercise interventions have uncovered mechanisms that upregulate and downregulate gene expression toward a beneficial state of health, especially in patients with metabolic syndrome, obesity, and type II diabetes. Increased physical activity and recommended diets balanced in omega-3/omega-6 ratios can be the pillars for health promotion and prevention of multiple chronic diseases.
6. All diseases have genetic predispositions. GWA studies are discovering genetic variants that influence risk of complex diseases. Missing from these studies is nutrient information essential for developing dietary advice for prevention and management of disease and for personalized nutrition. In addition to genetic variants, age, sex, health status, obesity, ethnicity, and other characteristics influence responses to diets.
7. As we advance our knowledge of gene-nutrient interactions, society will need to create or utilize appropriate social, ethical, legal, educational, and economic frameworks to gain the benefits of such knowledge.
8. Public health and regulatory processes will need to be established to define when genomic discoveries such as gene/nutrient disease associations are ready to be evaluated as potential tools to improve health screening and recommended dietary values (76).

At present, in terms of public health, certain dietary recommendations can be made at the population level.

1. Recommendations of caloric intake must always be calculated and considered together with energy expenditure. For example, the genomic-nutritional studies of the FTO gene variants in children show that overeating rather than decreased energy expenditure is what leads to early obesity.
2. Diets must be balanced in the omega-6 and omega-3 essential fatty acids to be consistent with the evolutionary understanding of the human diet. This balance can best be accomplished by decreasing oils rich in omega-6 fatty acids (corn oil, sunflower, safflower, cottonseed, and soybean oil) and increasing oils rich in omega-3s (canola, flaxseed, perila, chia, and olive oil, which is particularly low in omega-6).
3. Eat fish twice a week.
4. Eat more fruits and vegetables (7 or more portions) and vitamin D (1500–2000 U.I.) daily.
5. Eat lean meat and poultry.
6. Restrict salt intake, especially for those with a family history of hypertension, which could be refined with genotypes. Family history is still an important aspect of public health practice of disease prevention at the family level [see Valdez et al. (89), in this volume].

DISCLOSURE STATEMENT

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