



Personalizing our diet to improve our health: the potential impact of nutrigenomics



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'Nutritional genomics is a developing field that promises us the ability to personalize our diet to improve our health, based on individual genetic makeup.'

The data from the Human Genome Project [1] have revolutionized medical research through documentation of individual variation in gene sequences and identification of SNPs and their functional effects, thereby providing an opportunity to elucidate their role in chronic diseases. Nowhere are the changes more pronounced than in the field of drug development, which uses pharmacogenomics [2,3], a study of how individual genetic makeup might help in predicting drug efficacy and potential side effects. By incorporating genotyping in the early stages of the drug-development process, pharmaceutical companies could perhaps avoid the possibility of late withdrawal of blockbuster drugs from the market. In the long run, genotyping studies could save millions of dollars in drug-development costs and also help to design drugs targeted to a given population group with minimal side effects. If we can choose the right drug based on our genetic profile, what is next on the horizon? The answer: nutritional genomics [4,5].

Nutrigenetics, nutrigenomics & metabolomics

Nutritional genomics is a developing field that promises us the ability to personalize our diet to improve our health, based on individual genetic makeup. It consists of two subdisciplines:

- Interaction of dietary components with the genome and their subsequent effect on the phenotype as evaluated by proteomic and metabolomic markers (nutrigenomics);
- Understanding gene-based differences in our response to dietary components (nutrigenetics).

In the scientific literature, the terms 'nutrigenomics' and 'nutritional genomics' are often used interchangeably and warrant establishment of a uniform nomenclature. The significance of nutrigenomics and nutrigenetics in health and

disease and their role in the emerging area of metabolomics (metabolite analysis) are discussed in two excellent reviews by German *et al.* [6,7]. These authors raise some fundamental questions regarding the role of genetic differences in metabolic diversity, its effect on specific metabolic needs and identification of discriminating biomarkers of disease among various groups. What is very clear from these review articles is that nutrition and nutritional genomics will play a critical role in the development of metabolomics.

Common genes of nutrigenetic interest

Despite the identification of numerous SNPs that are of interest from the nutrigenomic point of view, translation of these observations into specific nutrigenetic mutation sites that are amenable to dietary manipulations are only beginning [8]. The two SNPs in the methylene tetrahydrofolate reductase (*MTHFR*) gene (consisting of C677T with a C to T substitution, and A1298C with an A to C substitution at position 1298) are the best-studied examples of nutrigenetics [9,10]. These *MTHFR* gene SNPs cause reductions in 5-methyl tetrahydrofolate, a cofactor for *MTHFR* enzyme activity, causing increased plasma homocysteine, which is a risk factor for venous thromboembolic disease, ischemic arterial disease and neural-tube defects [11,12]. Supplementation with folic acid helps to overcome the negative health effect of these SNPs in the *MTHFR* gene [13,14]. There are a number of examples in lipoprotein metabolism, particularly with *apo-E*, *apo A-1* and hepatic lipase genes and their interaction with dietary fat intake [15–19]. For example, in response to a high-fat diet, subjects with *apo-E4* respond negatively in terms of increased risk for coronary heart disease [16,17]. In subjects with a G to A mutation in the promoter region of the *apo A-1* gene, greater amounts of polyunsaturated fat were required to raise plasma high-density lipoprotein levels compared with subjects with 'normal' genotypes [18]. With regard to obesity-related genes, leptin and leptin-receptor gene mutations have emerged as leading candidates towards predicting obesity [20–23]. Among other candidates, mutations in the melanocortin-4 receptor, melanocortin-5 receptor and

neuropeptide Y (NPYY5R) receptor genes are also subject to increased attention [24–26]. Other important areas for nutrigenetic investigations include oxidative stress, inflammation and sterol absorption, which are amenable to nutritional manipulation. The readers are also referred to excellent reviews by Ordovas [15], Kornman [27], Loktionov [28] and Masson *et al.* [29] for a good understanding of potential SNPs that come under the umbrella of nutritional genomics.

Personalized nutrition in action

Many of the chronic diseases, such as atherosclerosis, hypertension, Type 2 diabetes and obesity, result from metabolic imbalances and all contribute as major risk factors towards coronary heart disease [30–32]. Oxidative, inflammatory and thrombogenic mechanisms also contribute to the development of atherosclerosis [33–36]. Nutrients play an important role in influencing factors responsible for this metabolic imbalance, and nutritional genomics will determine what (and how) nutrients will produce the desired impact on metabolic balance as influenced by individual genetic makeup (personalized nutrition). Plasma cholesterol control will be used as an example to illustrate how this risk factor is amenable to selected diet modification using nutraceuticals based on nutritional genomics. Recent research has defined the role of ATP-binding cassette transporters in cholesterol absorption [37,38] and identified polymorphisms (C1950G) in the *ABCG5* gene that influence differences in absorption and response to dietary cholesterol in some individuals. In individuals carrying this mutation, the use of a dietary therapy to inhibit cholesterol absorption will be useful. One of the choices, for example, would be phytosterol esters. Phytosterol esters, currently sold in the form of margarine Benecol® in US grocery stores, represent one of the new line of clinically tested products shown to decrease cholesterol absorption and lower plasma cholesterol [39]. This ester consists of a C-29 saturated plant sterol (sitosterol) esterified to fatty acids, which can also be incorporated into foods such as milk and yogurt [40]. This is how nutrigenomics will enhance our ability to tailor diet to improve health. These developments coincide with the renewed public interest in developing cost-effective ‘dietary therapy’ for lifetime maintenance of optimal plasma cholesterol levels, although drug therapy (a variety of statins) is available to control plasma cholesterol. It is interesting to note that the market for fortified and functional foods is projected to grow by at least 7% each year from

US\$47 billion recorded in 2002 [41]. Using purified and clinically tested nutraceuticals will also eliminate health concerns regarding the risk of toxicity and potential interaction with other drugs associated with the use of dietary supplements and herbs [42,43]. It is hoped that a number of well-tested nutraceuticals targeted to other sites of metabolic imbalance will find their way into the market place.

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Nutritional genomic principles in some instances can interplay with pharmacogenomics. The best example of this is the increased risk of deep-vein thrombosis and stroke associated with oral contraceptive use in women [44,45]. This risk is even greater for those women with prothrombin and factor V Leiden mutations [46,47]. In the Women’s Health Initiative trial, hormone-replacement therapy was shown to have negative effects on the risk of stroke, venous thrombosis and cardiovascular disease [48,49]. Recent studies suggest potential interactions between estrogen therapy and thrombophilic factor V Leiden and prothrombin gene mutations, which result in enhanced thrombosis and coronary heart disease risk [50–52]. Accordingly, young women taking oral contraceptives or postmenopausal women receiving estrogen-replacement therapy carrying thrombophilic mutations (factor V Leiden, prothrombin and PAI-1 mutations) could benefit from nutraceuticals that could reduce or control thrombosis risk. Although aspirin (and other NSAIDs) can prevent platelet aggregation and reduce thrombotic risk, many have side effects, including gastrointestinal bleeding [53]. Furthermore, there is increased public interest in the use of dietary supplements and the availability of well-tested nutraceuticals. Studies from our laboratory and others exploring potential nutraceuticals from the popular Amazonian herb guarana (*Paulinia cupana*, *Saponidaceae*) noted that guarana contains a powerful inhibitor of platelet aggregation and thromboxane synthesis [54]. Purified nutraceutical fractions from guarana preparations could offer considerable benefit as a dietary supplement through reduction in platelet reactivity in thrombosis, atherosclerosis and stroke [35,36], especially in subjects receiving hormone-replacement therapy [55].

Personalized medicine & nutrigenomics: what does the future hold?

How will nutrigenomics impact personalized medicine? I envision the following sequence of events:

- Genotypical analysis (using sophisticated genetic technology) of a 'nutrigenetic SNP panel' that depicts specific health risks in populations will become routine. This will be analogous to the 'thrombosis SNP panel' currently used to assess risk of thrombosis [56];
- Nutrigenetic SNP data will then be reviewed by clinical nutrition/dietetics/medicine experts;
- Appropriate nutraceuticals (or functional foods) will be recommended as part of preventative medicine therapy to control risk factors.

The nutraceutical market will open up on three distinct fronts:

- Dietary supplements, as is in common use now for vitamins;
- Nutraceuticals incorporated into a variety of food products, such as juices, cereals, snacks and spreads;
- Whole functional foods (e.g., a margarine such as Benecol).

Nutraceuticals based on individual genotype will have three major goals:

- Help alleviate a metabolic imbalance
- Decrease the amount of pharmaceutical use
- Ultimately reduce individual drug and healthcare costs

'We can all benefit by learning about our finer differences in response to diet and drugs and then applying this knowledge to the successful practice of personalized medicine.'

Finally, it is important to note that while more than 99% of the human DNA sequences are similar across ethnic and cultural lines, there may be differences in genes that contribute to the initiation and/or progression of metabolic diseases. Populations that inhabited and evolved in different parts of the world may have environmental imprints on their genetic makeup that could influence response to nutrients. We can all benefit by learning about our finer differences in response to diet and drugs and then applying this knowledge to the successful practice of personalized medicine.

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