

DISEASE PREVENTION THROUGH NUTRITION

Applying genomic technologies to nutrition offers innovative strategies to unravel interactions between nutrients and genes, and paves the way towards preventive personalised nutrition

The growing prevalence of obesity, as well as the alarming rise in its associated pathologies such as hypertension, diabetes and heart disease, reflects a mismatch between our modern diet, sedentary lifestyle and our genetic background.

Indeed, over millions of years our thrifty genome has been optimised by, and for, a food environment that was considerably different from the present day one. The major changes, which occurred through the Neolithic transition from hunter-gatherer to breeder-farmer and later during the 19th Century waves of industrialisation, are relatively recent if one considers the evolutionary timescale of the human species. Meanwhile, our genome has remained extremely similar, which has led to the emergence of a frequent phenotype characterised by both excess of fat and micronutrient deficiencies due to increased intake of poor quality calorie-rich food and insufficient physical activity.

Emergence of nutritional genomics

At the turn of the millennium, high performance genomics associated technologies applied to nutritional sciences gave birth to nutritional genomics, a revolutionary research area that investigates the bidirectional interactions between genes and nutrition.

Nutritional genomics comprises two distinct, but complementary, approaches: nutrigenetics and nutrigenomics. Nutrigenetics aims to identify the hereditary foundations of differences in inter-individual responses to diet, which may promote nutrition linked diseases, while nutrigenomics focuses on defining whole genome 'dietary signatures'. These signatures characterise the action of nutrients on the structure and expression of the human genome and, ultimately, their impact on health. They consist of changes observed at the level of genes (genomics and epigenomics), gene transcripts (transcriptomics), and proteins (proteomics), as well as the dynamic profile of metabolites, the intermediates and products of metabolism (metabolomics).

How do nutrients control our genes?

Feeding represents the strongest interaction with our environment. Food components are generally classified into macronutrients (fats, carbohydrates, and proteins), which are required in high amounts and mainly function as fuel or calorie providers, and micronutrients (vitamins, minerals, phytonutrients, essential amino acids, and fatty acids), which are needed in much smaller quantities, but are essential for regulatory processes. Micronutrients can modulate gene activity at different levels. Some of them, such as fatty acids, some vitamins and oligoelements activate or repress key regulatory

factors of gene expression. Nowadays, transcriptomics tools can identify diet induced changes in gene expression at the level of the entire genome.

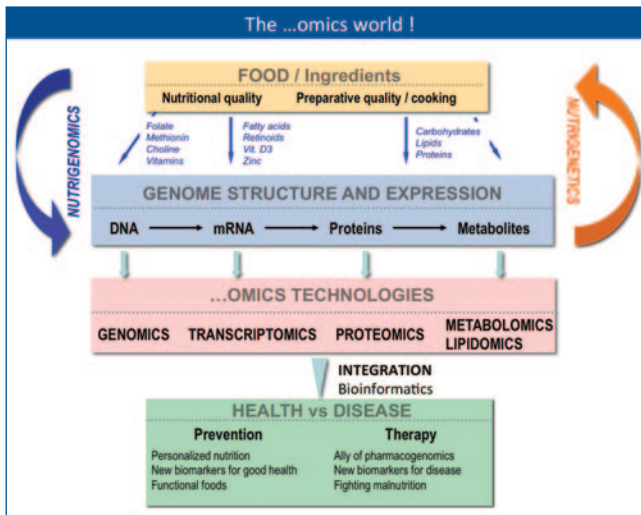
Other micronutrients, such as folic acid, choline, and B-group vitamins, can modulate gene expression through epigenetic modifications, that is by adding or removing molecular tags to the DNA or histones (the proteins around which DNA wraps). These tags modify the accessibility of genes to the transcription machinery without changing the primary DNA sequence. Although usually reversible, epigenetic tags may turn out quite persistent over life and even be passed on up to third generation offspring. Thus, they can influence disease susceptibility. Epigenetic modifications occurring throughout life keep track of specific environmental events, imprinting them 'on top of' (the meaning of the Greek prefix *epi*) the basic DNA sequence.

Excesses or deficiencies in some micronutrients (such as vitamins and oligoelements) can directly damage DNA through strand breaks, nucleotide deletions or changes, and telomere shortening. The impact of micronutrient deficiencies on genome integrity is estimated to be on the same order of magnitude as that of ultraviolet radiation. Indeed, some oligoelements are crucial factors in replication accuracy, resistance to oxidative stress, and effectiveness of DNA repair mechanisms.

In addition to our own human genome, we play host to a supplemental genome, called the metagenome, which encompasses the genomes of all the micro-organisms living in our digestive tract. The metagenome contains approximately 150 times more genes than our eukaryotic genome and its activity is also influenced by our diet. The first insights into the rapidly expanding field of metagenomics suggest that personalised nutrition could play a role in restoring gut microbiota homeostasis, which is thought to be a crucial factor for good health. Thus, nutrigenomics ultimately requires a metagenomic approach in order to achieve a systematic understanding of how nutrients impact health.

Individualised nutrition

By unravelling interactions between nutrients and specific genes, nutritional genomics paves the way toward personalised nutrition and predictive medicine. A few years from now, it may well be possible to formulate precise dietary recommendations that target individual nutrition needs in accordance with genotype, age, gender, as well as professional and physical activity.



Application of nutritional genomics to the food industry will lead to the production of nutrigenomic foods, also called functional foods, that consist of tailored preparations designed to generate specific genomic signatures adapted to the nutritional needs of subgroups of people, or even of entire populations, of the same ethnic origin. The innovative step will come from combinations of ingredients that have been shown to induce specific synergic effects on key metabolic functions essential for either maintaining good health or preventing the onset of metabolic disorders.

As an example, beneficial effects of Actigenomics' product Lipistase® (which contains plant and fish oils, vitamins and oligoelements) on body weight gain, hypertriglyceridemia, liver steatosis, and atherosclerosis have been observed in mice models. These findings suggest that Lipistase could become a novel and cost effective combinatorial micronutrient-based strategy now evaluated in randomised clinical trials.

Disease prevention is the first area in which nutrigenomics is expected to deliver the most beneficial outcomes, particularly in the context of chronic non-communicable diseases and ageing associated diseases. Indeed, nutrigenomic functional foods are likely to achieve their full preventive potential if included in the diet early enough in the development of dysfunctions, before medication is needed. In parallel, benefits of nutrigenomic foods are also awaited from their combined use with medical treatments. A clever collaboration of nutrigenomics and pharmacogenomics – the science of drug-gene interactions – may be of great interest for optimisation of individualised therapeutic strategies. Not only does this apply to chronic disorders linked to diet and lifestyle habits, but also to health conditions that require heavy daily medication and in which the low immune state of the patient necessitates closely monitored nutritional supplementation, such as cancer and AIDS.

Furthermore, cleverly combined active ingredients may offer a cost effective solution for disadvantaged populations that suffer from the disastrous consequences of malnutrition by enhancing macronutrient absorption and reinforcing the immune system, thus averting repeated episodes of infection in malnourished people.

Challenges of nutrigenomics

The short-term main objectives of nutrigenomics research are to assess new nutrient-gene interactions in order to identify subpopulations with common genetic susceptibilities, and/or presenting biological markers that indicate early stages of dysfunction. Ideally, such markers would be detected in bodily fluids and reflect a range of minor changes in gene or protein expression profiles, which, taken together, will have substantial predictive value. If applied broadly and made accessible to those who would most benefit from it, the individualised approach of nutrigenomics is meant, in the long-term, to enhance public health at populations level.

These perspectives raise a whole range of ethical and societal issues regarding genetic testing, such as data acquisition and privatisation, test standardisation, and the appropriate way to disclose test results to individuals. In order to prevent misuse and consumer mistrust, it is first essential to consider the limits and consequences of nutrigenomic applications and to establish legal regulations and an ethical framework. Personalised, genotype-based nutrition will also affect people's relationship with the economic and social dimensions of food. This will mean greater responsibility for individuals in the way their eating habits evolve.

Conclusions

The ultimate purpose of nutritional genomics is to prevent diseases or treat them at early stages, if possible before the onset of symptoms, via personalised, partly genotype-based dietary recommendations. Fulfilment of this objective will shape nutrition into an efficient tool that can be used against the alarming rise in obesity and diet associated metabolic disorders worldwide. Furthermore, the development of functional nutrigenomic foods will address whole population health problems, such as nutrient deficiencies, immune frailty, and age related, as well as degenerative, disorders.

Because of its revolutionary approach and numerous fields of application, nutrigenomics stands at the crossroads between medicine, biology, human science, and the food industry. All of these areas will benefit from joining forces to promote nutrigenomics as a vector for scientific and social innovation.



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