

# Nutritional Genomics

Recent dynamic development of genetics and its adjacent fields of study on one hand open the so far unthinkable perspectives of the basic and clinical research but, on the other hand, it bears the risk of too one-sided "genocentric" view of pathogenesis of human diseases and, in general, of all biological processes. Nevertheless, more complex view and approach is needed in perspective of today's sweeping pandemics of obesity and other western-type society diseases. The pandemics of obesity, cardiovascular disease, diabetes, etc. emerged only recently so we can't presume that important changes of the genome are to blame. The more probable cause of the above mentioned diseases can be found in the change of the outcomes of genome x environment interactions. The environment is represented mainly by the lifestyle and diet, and as such it indeed dramatically changed during the last century in both qualitative and quantitative ways of physical activity, stress levels and diet.

On the empirical level it is well known that the quantity as well as the diet composition affects the onset, incidence, severity and progression of majority of chronic diseases. Opposed to the pharmacotherapy with well defined doses and target structures and mechanisms of action, our diet consists of heterogeneous mixture of many biologically active substances, some of which can be direct ligands of receptors affecting transcription of huge amount of genes (1). Moreover, it is becoming evident that maternal diet during the pregnancy is important, as it "metabolically programs" through epigenetic modulations the homeostatic systems of the fetus (3)

Thanks to the development of methods in molecular genetics and bioinformatics it is now feasible to pursue integrative approaches in the field of study of such prevalent diseases as e.g. metabolic syndrome, and to integrate the initially opposing principles of "nature vs. nurture" into the unified paradigm of the nutritional genomics.

## Nutritional genomics and its definition

The fact, that common diet contains many bioactive substances that can through the interaction with receptors activate or modulate the transcription of target genes or directly cause the rearrangement of chromatin structure, is widely accepted, but not often recognized in the design and interpretation of genetic and epidemiologic studies. The studies that follow the effect of a certain diet often disregard the possible effect of genetic variability within the studied cohort, on the other hand, some studies analyzing the effect of candidate gene polymorphism on the studied trait (for example blood pressure, obesity) do not include the diet interference, which can dramatically influence the resulting association. Nutritional genomics aims to resolve this evident discrepancy. In a certain parallel to pharmacogenomics, the nutritional genomics focuses on the bioactive substances found in regular food and how those substances affect the balance between health and disease via the interaction with the individual's genome. These are 5 basic principles of nutrigenomics (5):

1. Substances contained in the food (micro- and macro-nutrients) can directly or indirectly affect the human genome through changes in its structure and gene expression.
2. Under certain circumstances and in some individuals the diet can be an important risk factor for the development of the number of diseases.
3. Some genes regulated by active substances in the diet probably play a crucial role in the onset, incidence, progression and severity of the disease.

4. The degree to which diet influences the balance between health and disease may depend on individual's genetic makeup.
5. Nutritional intervention is based on the knowledge of individual's nutritional status and needs as well as genotype (individualized nutrition) and can be used for prevention, mitigation or healing the chronic diseases.

## **The tools of nutrigenomics**

Nutrigenomics as a new and independent field of study emerged thanks to the technological possibilities that enable to analyze the effect of food intake on the whole genome. This whole-genome analysis gave rise to pharmacogenomics and functional genomics as well. One of the important tools of nutrigenomics is **gene expression profiling** - at transcriptome level by expression cRNA or cDNA chips, similar approaches were developed for expression analysis on the level of proteins (proteome - mainly the 2D electrophoresis and many forms of mass spectrometry) and on the level of metabolites (metabolome). Expression profiles of genes, proteins and metabolites responding to the given diet constituent or to the nutritional regimen are considered here as "diet signatures" that are further analyzed on the levels of specific cells, tissues and whole organisms in order to understand the effect of nutrition on homeostasis. Detailed aspects of this issue are beyond the scope of this article, for further reading please consult the recent reviews (6,7). In order to perform statistically robust experiments that will give reproducible data, it is necessary to solve the two main questions that the genetic epidemiology within the field of nutritional genomics was not able to deal with fully yet. We need to analyze as fully as possible both parts of nutrigenomic interaction, physical and chemical characterization of the food components as well as target structures and polymorphisms within the genome.

Except for rare cases like relative population isolates, where the genetic variability is limited, it is hard to analyze in detail the genetic components of complex metabolic diseases without including the interaction with the environment (with diet in case nutrition genomics). Factors limiting the genetic analysis include genetic heterogeneity of general human population or variable penetrance of complex traits (7). The example of relatively genetically isolated population is the religious sect of Hutterites. It was founded in 16th century in Tyrolean Alps. In next two centuries it had grown in Russia from 120 members to more than 1000. In 70s of 19th century 900 members of this sect immigrated to South Dakota in United States. Nowadays there are about 35 000 of them living in more than 350 community farms. Not only that thanks to genealogical analysis we can identify 90 common ancestors of nowadays Hutterites, but also their uniform lifestyle including the uniform diet prepared according to the traditional recipes is a great advantage for nutrigenomic studies (8). The relevance of findings obtained in population isolates remains questionable though, especially in terms of extrapolation of the obtained data to general population.

The fundamental approach in nowadays gene x environment interaction studies is the utilization of genetically defined mammalian models, mainly inbred strains of mouse and rat (e.g.ref.9). The evident advantages of utilization of animal models include the possibilities of selective mating leading to genome modifications, environment standardization and the possibility to repeat the experiments. Thanks to methods of comparative genomics it is then possible to integrate the relevant observations of gene environment interactions of both human and animal studies (fig.1). and then create "maps" of genes whose variants play role in different response to dietary compounds in the same fashion as there are gene "maps" of candidate genes for obesity (10) or hypertriglyceridemia (11). With sufficient marker

coverage of the whole genome and with sufficient number of polymorphism data (either single nucleotide polymorphisms - SNPs or haplotype blocks generated by international consortia (12)), the basis for the prediction of many nutrigenomic interactions will be laid. This effort should end up with designing a specific form of DNA chip for testing many thousands of polymorphisms in the genes that will be connected with detrimental reaction to the specific nutrient or to the quantity of a nutrient at the same time. Even before having this specific chip at hand, it will be probably feasible to identify new biological markers that could be used as indicators of potential detrimental or beneficial effects of the diet component. This information will be used in prevention as well as treatment of the disease, where nutrigenomic interactions play an important role.

## **Nutrigenetic interactions**

Classical example of nutrigenetic interaction leading to the clinical manifestation is persisting tolerance of lactose in adult age. Point mutation C13910T emerged probably 9000 years ago in north European population and caused long-term expression of lactose hydrolase and prevented thus the natural gradual loss of function of this enzyme leading to physiological hypolactasia in adulthood (13). Except for this "static" interaction there are also "dynamic" interactions that lead to different responses to the dietary change according to the genetic makeup of the individual. During the follow-up of men cohort in Czech MONICA study it was found that in response to dramatic dietary change between years 1988 - 1996 only the carriers of CC-204 variant of cholesterol-7 $\alpha$ -hydroxylase (CYP-7A1) gene reduced the cholesterol levels. The carriers of AA-204 variant of the gene were resistant to the dietary changes (14). It is also necessary to have in mind the gene-gene interactions, the overall genetic makeup on which the given allele operates as it can significantly modulate the given phenotype. The effect of a given allele is henceforth more easily studied on genetically defined models (15, 16). Haluzík et al. (16) verified this concept in a study where the introgression of mutation ob/ob of the leptin gene to the genome of two distinct mouse strains C57BL/6J and FVB/N caused significantly different manifestation of insulin resistance under identical dietary conditions.

In real life situations, the interactions can be even more complicated as the pharmacotherapy will influence the gene-diet interactions and the phenotypical outcomes. This dietary modulated pharmacogenomic interaction was recently described in a system of several genetically defined animal models of insulin resistance and dyslipidemia. We observed a significant difference in antidiabetic action of rosiglitazone on metabolic parameters. This action was dependent on dietary combination of carbohydrates and fats in diet and the genetic predisposition of tested individual (15, 16).

## **Perspectives: individualized diet**

As suggested above, nutrigenomics is just in the very beginning of its existence. Only large and systematic studies will determine how important nutrigenomics will be in the future clinical practice. The final goal of nutrigenomics is to find an optimum dietary regimen for a given individual respecting not only the quantitative and qualitative nutritional needs and health status, but also the genetic predispositions in order to prevent the onset of many western-type diseases, or to help to cure them more effectively.

## **Links**



The European Nutrigenomics Organisation <http://www.nugo.org/>

## Literature

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