Nutrigenomics and nutrigenetics – are they the keys for healthy nutrition?

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„Food and nutrition in 21st century”, Warsaw, 8-9.09.2011
Basic definitions

Nutrigenomics – analyzes the effects of bioactive food components (nutrients and non-nutrients) on gene expression

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From a nutrigenomic perspective bioactive food components are **dietary signals** that are detected by the cellular sensor systems (e.i. PPARγ and RXR receptors) that influence gene expression, protein synthesis and metabolite production.

From this point of view **genes** are **dietary targets**.

**Patterns of gene expression, protein synthesis and metabolite production** in response to particular nutrients can be considered as **dietary signatures**.
Nutrigenomics seeks to examine **these dietary signatures** in specific cells, tissues and organisms and to understand how nutrition influences homeostasis.

Nutrigenomics aims also to **identify the genes that influence the risk of diet-related diseases on a genome-wide scale** and to understand the mechanisms that underlie these genetic predispositions.

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Basic definitions (cont.)

Nutrigenetics – analyzes the effect of genetic variation on dietary response

Genetic variation between individuals results from numerous differences in nucleotide sequences within their genome: single nucleotide polymorphisms (*the most common form of genomic variation: in the human genome > 10 millions SNP*), copy number variations (CNV), deletions-insertions of single nucleotides or gene fragments, substitutions and inversions.

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## Nutrigenetic analysis of SNPs within some CVD-related genes

<table>
<thead>
<tr>
<th>CVD Risk Factor</th>
<th>Gene</th>
<th>SNPs</th>
<th>Genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipids</td>
<td>APOAI</td>
<td>-75G→A</td>
<td>GA</td>
</tr>
<tr>
<td>Lipids</td>
<td>APOC3</td>
<td>3175C→G</td>
<td>GG</td>
</tr>
<tr>
<td>Lipids</td>
<td>APOE</td>
<td>ε2, ε3, ε4</td>
<td>2, 3</td>
</tr>
<tr>
<td>Lipids</td>
<td>CETP</td>
<td>279G→A</td>
<td>GG</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>ACE</td>
<td>Ins/Del</td>
<td>ID</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>AGT</td>
<td>-6C→A</td>
<td>AA</td>
</tr>
<tr>
<td>Inflammation</td>
<td>IL1B</td>
<td>-511C→T</td>
<td>TT</td>
</tr>
<tr>
<td>Inflammation</td>
<td>IL6</td>
<td>-174G→C</td>
<td>GC</td>
</tr>
<tr>
<td>Methylation (folate)</td>
<td>MTHFR</td>
<td>677C→T</td>
<td>TT</td>
</tr>
<tr>
<td>Methylation (B12)</td>
<td>TCN2</td>
<td>776C→T</td>
<td>CT</td>
</tr>
</tbody>
</table>

CVD – cardiovascular diseases

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Copy-number variations (CNVs) are alterations of the DNA of a genome that results in the cell having an abnormal number of copies of one or more sections of the DNA. This variation accounts for roughly 12% of human genomic DNA and each variation may range from about one kilobase (1000 bases) to several megabases in size. CNVs contrast with SNPs, which affect only single nucleotide.

Alleles containing 0-13 active gene copies have been described, and one can assume that copy number variation may account for even 25% individual variation in response.

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Mechanisms by which nutrients influence gene expression:

1. Regulation of transcription factors and transcription process
Mechanisms by which nutrients influence gene expression:

2. Regulation of chromatin structure and DNA susceptibility to transcriptional machinery

*(how certain genes are switched on or switched off – nutri-epigenetics)*

Gene switched on:
- Active chromatin
- Unmethylated cytosines
- Acetylated histones

Gene switched off:
- Silent chromatin
- Methylated cytosines
- Deacetylated histones

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The two main components of the epigenetic labeling:

- DNA methylation: methyl marks added to one of DNA bases (cytosine) repress gene activity
- Histone modification: A combination of different molecules attached to the "tails" of histones alters activity of the DNA wrapped around them.

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Folate-rich diet influences DNA methylation process and can switch off some critical genes. **Folate** and **vitamin B12** contribute to generating 5-methyltetrahydrofolate (5-MTHF), which provides the methyl group for synthesis of methionine and SAM, the universal methyl donor of biological methylation. **DNA methylation inhibits gene expression.**

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**Folate-rich diet** of mother-mouse results in methylation of the IAP sequence in the genome of the offspring and the *agouti* gene silencing. Result: **brown color of child coat.**

**Folate-deficient diet** of mother-mouse results in hypomethylation of the IAP sequence and active *agouti* gene leads to a **yellow coat color, obesity and tumors.**
Mechanisms by which nutrients influence gene expression:

3. Prevention of DNA damage

The micronucleus assay in cytokinesis-blocked lymphocytes is currently the best validated biomarker for nutritional genomic studies of DNA damage.
Moderate folate deficiency within the physiological range causes as much DNA damage in cultured lymphocytes as ten times the annual allowed limit of exposure to X rays.

The typical plasma folate concentration is only 10–30 nmol/L, a level adequate to prevent anemia but insufficient to minimize chromosomal damage.

Michael Fenech, CSIRO Preventive Health National Research Flagship
Nutrigenetics and nutrigenomics can be useful for better understanding of nutrient-gene interactions and development of personalized nutrition strategies for optimal health and disease prevention.

„Personalized nutrition“ - a diet addressed to an individual and based upon her/his genotype, nutritional requirements and other factors (age and gender). It is expected that personalized nutrition will prevents diet-related chronic diseases.
How to achieve this goal?

1. Basic studies:
   - identification of next generation biomarkers

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How to achieve this goal?

1. Basic studies:
   - identification of SNPs-disease associations (Genome wide association studies – GWAS)

Genome-wide association studies – an approach for identifying genes that are associated with diseases. GWA studies allow to test hundreds of thousands of single-nucleotide polymorphisms (SNPs) for association with a disease in hundreds or thousands of persons.

Nearly 600 genome-wide association studies covering 150 distinct diseases and traits have been published, with nearly 800 SNP–trait associations reported as significant.

The Wellcome Trust Case Control Consortium: The Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature(2007), **447**: 661-684:

The article describes results of the GWA studies of 2,000 cases and 3,000 shared controls for seven complex human diseases of high importance: bipolar disorder (BD), coronary artery disease (CAD), Crohn’s disease (CD), hypertension (HT), rheumatoid arthritis (RA), type 1 diabetes (T1D), and type 2 diabetes (T2D).

Wellcome Trust Case Control Consortium (WTCCC) brought together over 50 research groups from the UK that are active in researching the genetics of common human diseases, with expertise ranging from clinical, through genotyping, to informatics and statistical analysis.
How to achieve this goal?

▪ determination of dietary reference values (e.g. recommended dietary allowance – RDA) for DNA damage prevention (see folic acid case!)

▪ application of new technologies to understand mechanisms of action of dietary factors and metabolites

Some of these studies and/or technologies are in their infancy while others are much more advanced. Therefore they differ in their validation status and applicability.
How to achieve this goal? (cont.)

2. Development of experimental approaches and technologies for studying nutrigenetics and nutrigenomics:

- sample handling and processing
- data collection and analysis (new bioinformatic tools)
- epidemiologic studies to examine the effects of dietary exposure and genetic variations in humans
- evaluation of evidence from nutrigenetic case studies

It is becoming evident that genetic background, age and gender can have an impact on nutritional requirements but translation of this knowledge is only practical in few cases (galactosemia, phenylketonuria).
Will public health be improved with personalized dietary recommendations?

- How costly will personalized nutrition be?
- Will people be motivated to use a personalized diet?
  At the moment, there is a degree of public confusion and resistance to messages that foster unpopular advice, such as ‘get more exercise’ or ‘eat less calories’.
- Will this approach be available only for rich and well-educated?
- How to educate people?

Main topics in the presentation are based on the review by Fenech et al.: „Nutrigenetics and Nutrigenomics: viewpoints on the current status and applications in nutrition research and practice” published recently in Journal of Nutrigenetics and Nutrigenomics (2011), 4: 69 – 89.

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Despite the great promise of nutrigenetics and nutrigenomics, there is still a long way to go before dietary recommendations based on results of nutrigenomic/nutrigenetic studies.

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