NUTRIGENOMICS

WHAT IN THE WORLD IS THAT?!

I THINK THAT'S LUNCH!!!

MEALTIME CONFUSION AT THE TOUR DE FRANCE

Mireia Viñas
Genomics
Overview

- Introduction
- Nutrigenomics
- Ethnic differences
- Nutritive effects
- Nutrigenetics
- Nutrigenetics and disease
- Conclusions
- Bibliography
Introduction

**Nutrigenetics** → Impact of genetic profile in the body response

**Nutrigenomics** → Influence of nutrients in gene expression

*Farhud et al.*
Introduction

• Dietary chemicals act on the human genome to alter gene expression

• On specific conditions and certain individuals, diet represent a risk factor for some diseases

• Diet-regualted genes act in different stages of chronic diseases

• Individual genetic background determines the degree at which diet mantains an equilibrium

• Dietary intervention to prevent, relieve or cure chronic diseases

Farhud et al.
Nutrigenomics

- Integration of high-throughput genomic tools with nutrition research

- Dietary effects on:
  - Genome stability
  - Epigenome alterations
  - RNA and microRNA expression
  - Protein expression
  - Metabolite changes

Table 2: Examples of the role and effect of specific micronutrients deficiencies on genomic stability (56, 57)

<table>
<thead>
<tr>
<th>Micronutrients</th>
<th>Role in genomic stability</th>
<th>Consequence of deficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vits C and E</td>
<td>Prevention of DNA and lipid oxidation.</td>
<td>Increased baseline level of DNA strand breaks, chromosome breaks, oxidative DNA lesions and lipid peroxide adducts on DNA.</td>
</tr>
<tr>
<td>Vit D</td>
<td>Antioxidant activity by increasing glutathione level in normal cell, induction apoptosis in cancer cells.</td>
<td>uracil misincorporation in DNA, increased chromosome breaks and DNA hypomethylation.</td>
</tr>
<tr>
<td>Folate and Vits B2, B6, B12</td>
<td>Maintenance methylation of DNA, synthesis of dTMP from dUMP and efficient recycling of folate.</td>
<td>Increased level of unrepaired nicks in DNA, increased chromosome breaks and rearrangement, sensitivity of mutagens.</td>
</tr>
<tr>
<td>Niacin, Nicotinic acid</td>
<td>Required as substrate for poly (ADP-ribose) polymerase which is involved in cleavage and rejoining of DNA and telomere length, Maintenance and DNA repair, Zn, required as a cofactor for Cu/Zn superoxide dismutase, endonuclease IV, P53 function, DNA replication and Zinc finger proteins such as poly (ADP-ribose) polymerase.</td>
<td>Increased DNA breaks and oxidation, elevated chromosomal damage rate.</td>
</tr>
<tr>
<td>Zinc, Manganese and Selenium</td>
<td>Mn, required as a component of mitochondrial Mn superoxide dismutase, Se, required as a component of peroxidases e.g. glutathione peroxidase.</td>
<td>Reduced DNA repair capacity, increased propensity for oxidative damage to mitochondrial DNA.</td>
</tr>
<tr>
<td>Iron</td>
<td>Required as a component of ribonucleotide reductase and mitochondrial cytochromes.</td>
<td>Reduced fidelity of DNA replication, reduced DNA repair capacity, chromosome segregation Errors, survival of genomically aberrant cells.</td>
</tr>
<tr>
<td>Magnesium, Calcium</td>
<td>Mg, required as a cofactor for a variety of DNA polymerases, in nucleotide excision Repair, base excision repair and mismatch Repair, essential for microtubule Polymerization and chromosome segregation. Ca, plays an important role in chromosome Segregation and is required for apoptosis.</td>
<td></td>
</tr>
</tbody>
</table>
Nutrigenomics

- Folate deficiency → uracil incorporation
- Uracil glycosylase → DSB leading to abasic sites
- Oxidative stress + folate deficiency
- Oxidized bases → abasic sites and DSB
- Low folate conditions → DSB within one cell division
Nutrigenomics

- Diet can cause epigenetic changes

- DNA methylation is dependent on bioactive food components

- Defects in DNA methylation:
  - Excessive telomere elongation
  - Homologous recombination between telomeres
  - Telomere fusion

C. Bull and M. Fenech
Nutrigenomics

• Calorie-restricted organisms:
  – live longer
  – have increased resistance to disease
  – physically age slower
  – postpones many signs of aging
Nutrigenomics

• TOR pathway influence in life span:
  – Decreased TOR signaling $\rightarrow$ extend life span of *Caenorhabditis elegans* (Vellai et al.)
  – Overexpression of dominant negative allele of TOR extends life span of *Drosophila* (Kapahi et al.)
  – Specific TOR inhibitor (Rampamycin) $\rightarrow$ increase in life span of mice (Harrison et al)

• mTOR inactivation $\rightarrow$ attenuation of global protein synthesis and decrease cellular load of erroneously synthesized polypeptides
Nutrigenomics

• Diversity in the inherited genome between ethnic groups and individuals → nutrient bioavailability and metabolism

• Differences in food/nutrient availability and choices → cultural, economical, geographical and taste perception

• Malnutrition affect gene expression → mutations at gene or chromosomal level
Ethnic differences

- Singapore → variability in response to a diet (Chinese, Malays and Asian Indians)

- Ethnic heterogeneity within homogeneous environments

Table 4: Age-standardized* prevalence of major factors influencing cardiovascular disease risk in 1998 by ethnic group

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Chinese Men</th>
<th>Chinese Women</th>
<th>Total Men</th>
<th>Total Women</th>
<th>Total</th>
<th>Malay Men</th>
<th>Malay Women</th>
<th>Total Malay</th>
<th>Indian Men</th>
<th>Indian Women</th>
<th>Total Indian</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetic mellitus</td>
<td>7.0 (5.7–8.2)</td>
<td>7.1 (5.9–8.3)</td>
<td>7.0 (6.2–7.9)</td>
<td>8.5 (6.1–10.8)</td>
<td>10.7 (8.9–12.5)</td>
<td>14.5 (11.3–17.6)</td>
<td>14.6 (11.6–17.6)</td>
<td>14.5 (12.4–16.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>13.4 (11.7–15.2)</td>
<td>12.7 (11.2–14.2)</td>
<td>13.1 (11.9–14.2)</td>
<td>19.3 (15.5–23.2)</td>
<td>19.0 (15.5–22.5)</td>
<td>19.2 (16.6–21.8)</td>
<td>10.5 (7.5–13.5)</td>
<td>15.6 (11.7–19.6)</td>
<td>13.0 (10.6–15.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>30.9 (28.3–33.4)</td>
<td>20.9 (18.9–23.0)</td>
<td>26.0 (24.3–27.6)</td>
<td>28.6 (23.8–33.5)</td>
<td>36.0 (31.5–40.4)</td>
<td>32.3 (29.0–35.5)</td>
<td>26.3 (21.1–31.4)</td>
<td>21.1 (17.1–25.1)</td>
<td>23.7 (20.4–27.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obesity</td>
<td>4.5 (3.4–5.6)</td>
<td>3.0 (2.2–3.8)</td>
<td>3.8 (3.1–4.4)</td>
<td>8.7 (6.0–11.4)</td>
<td>22.0 (18.2–25.8)</td>
<td>15.3 (12.9–17.6)</td>
<td>7.2 (4.1–10.3)</td>
<td>17.5 (13.4–21.5)</td>
<td>12.3 (9.7–14.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>High total blood cholesterol</td>
<td>23.3 (21.3–25.4)</td>
<td>20.1 (18.4–21.9)</td>
<td>21.8 (20.4–23.1)</td>
<td>38.4 (33.7–43.1)</td>
<td>29.4 (31.0–36.9)</td>
<td>34.0 (21.8–31.7)</td>
<td>26.7 (14.9–23.3)</td>
<td>19.1 (19.7–26.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking</td>
<td>23.4 (21.2–25.7)</td>
<td>3.3 (2.4–4.2)</td>
<td>13.5 (12.3–14.7)</td>
<td>42.9 (37.8–48.0)</td>
<td>3.7 (2.0–5.5)</td>
<td>23.6 (20.9–26.3)</td>
<td>29.3 (23.6–35.0)</td>
<td>0.8 (0.0–1.8)</td>
<td>15.3 (12.3–18.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regular exercise</td>
<td>19.1 (17.0–21.1)</td>
<td>12.4 (10.9–14.0)</td>
<td>15.8 (14.5–17.1)</td>
<td>23.5 (19.2–27.8)</td>
<td>14.9 (11.5–18.2)</td>
<td>19.3 (16.5–22.0)</td>
<td>31.2 (25.3–37.0)</td>
<td>18.7 (14.3–23.0)</td>
<td>25.0 (21.3–28.7)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*a*b See footnotes a–b, Table 3.

c Figures in parentheses are 95% confidence intervals.

d–h See footnotes d–h, Table 3.

Mak et al., Cutter et al.
Nutritive effects

- Availability of environmental nutrients:
  - determinant of growth and survival
  - optimal immune response

- Honey bees → pollen nutrition influence longevity, sensitivity to pesticides and resistance to pathogens

- Digital gene expression (DGE) between pollen feeding in normal and sick bees (varroa-parasited)

<table>
<thead>
<tr>
<th>Comparisons</th>
<th>Upregulated genes</th>
<th>Downregulated genes</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>V+P+/V+P−</td>
<td>1,331</td>
<td>1,140</td>
<td>2,471</td>
</tr>
<tr>
<td>V+P+/V+P−</td>
<td>146</td>
<td>1,677</td>
<td>1,823</td>
</tr>
<tr>
<td>V+P+/V−P−</td>
<td>169</td>
<td>2,474</td>
<td>2,643</td>
</tr>
<tr>
<td>V+P+/V+P+</td>
<td>25</td>
<td>3,789</td>
<td>3,814</td>
</tr>
</tbody>
</table>

Genes were considered significantly differentially expressed between two treatments if their associated Q-value < 0.01.

Alaux et al.
Nutritive effects

- Vitellogenin (Vg) $\rightarrow$ egg production and antioxidant functions
- Varroa parasitism decrease Vg levels in P+ but worst in P-
- Prophenoloxidase (PPO) $\rightarrow$ insect immunity
- Varroa inhibition $\rightarrow$ immunity suppression, no pollen effect
- *Drosophila* ortolog *spaetzle* $\rightarrow$ signalling pathway against fungi and bacteria
- Increased in V-P+ bees $\rightarrow$ pollen enhance immune functions

Alaux *et al.*
Nutrigenetics

- Glutatione peroxide gene → Pro/leu at codon 198 increased risk of lung cancer

- Manganese super oxide dismutase (MnSOD) → Val/Ala high risk of breast cancer (Trujillo et al.)

- Methylene tetrahydrofoululate reductase (MTHFR) → Ala/Val reduced risk for folate-related pathologies (Stover)
Nutrigenetics

- Caffeine-coffee $\rightarrow$ increased risk of heart attack and myocardial infarction for carriers of slow activity of CYP1A2 isoform (El-Schemy)

- Apolipoprotein A-1 (APOA1) $\rightarrow$ highly polymorphic coding gene with a specific SNP

- A allele $\rightarrow$ increased HDL cholesterol

- APOA1 and HDL $\rightarrow$ protective factors for cardiovascular disease

Mata et al., Ordova et al.
Nutrigenetics and disease

- Butyrate → originated by bacterial fermentation in colorectal cancer cells
- Butyrate treatment → induce apoptosis and inhibit proliferation
- Proteomics and gene expression → identification of butyrate mechanisms

Apoptosis and proliferation in colorectal cancer cell lines in response to increased butyrate concentration

Fenech et al.
## Nutrigenetics and disease

<table>
<thead>
<tr>
<th>Alzheimer</th>
<th>Coeliac disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Apolipoprotein E → cholesterol carrier in the brain</td>
<td>• Inability to tolerate gluten-containing foods</td>
</tr>
<tr>
<td>• Genetic variation in gene encoding apolipoprotein E4 → risk for Alzheimer’s disease</td>
<td>• Carrying the gens does not determine disease development</td>
</tr>
<tr>
<td>• Development of preventing strategies for genetic predisposition people</td>
<td>• HLA-DQ (DQ2 and/or DQ8) genes → necessary but not sufficient</td>
</tr>
</tbody>
</table>

*McGough and Cummings*
Nutrigenetics and disease

Obesity

Table 5: Weight and BMI loss (or gain if negative) in the two groups.

<table>
<thead>
<tr>
<th>Time point</th>
<th>Non tested group</th>
<th>Nutrigenetic group</th>
<th>P &lt; *</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>weight as % of baseline</td>
<td>Δ kg</td>
</tr>
<tr>
<td>baseline</td>
<td>43</td>
<td>100.0%</td>
<td>4.77</td>
</tr>
<tr>
<td>30–45</td>
<td>35</td>
<td>95.4%</td>
<td>8.42</td>
</tr>
<tr>
<td>90–100</td>
<td>23</td>
<td>92.2%</td>
<td>6.94</td>
</tr>
<tr>
<td>100–300</td>
<td>36</td>
<td>93.4%</td>
<td>6.94</td>
</tr>
<tr>
<td>&gt; 300</td>
<td>22</td>
<td>103.2%</td>
<td>-2.74</td>
</tr>
</tbody>
</table>

Weight at follow-up as % of baseline values are shown along with the percentage of individuals in each group who lost weight (regardless of the amount).

* The p-value refers to the analysis of variance comparing the change in BMI between the non-tested and nutrigenetic groups.

Arkadianos et al.
Conclusions

• The ultimate aim of nutrigenomics is to understand how nutrition influences metabolic pathways and homeostasis and develop dietary-interventional strategies.

• The genetic background, gender and life stage have an impact on nutritional requirements.

• Responses between individuals to dietary changes differ considerably → need to combine nutrigenetic-based advice and ‘omic’ biomarkers.

• Intervention based on knowledge of nutritional requirement can be useful to prevent, mitigate or cure chronic diseases.
Bibliography

• Kapahi et al. Regulation of Lifespan in Drosophila by Modulation of Genes in TOR Signaling Pathway. Division of Biology 156-29.
Thank You for your attention!