Nutrigenomics and Nutrigenetics
The Scientific Context

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Nutrigenomics

Effect of food and nutrients on the genome expression
Risk: Obesity, Diabetes type 2 etc..

Nutrigenetics

Impact of genetics on the food and nutrients effects

Biomarkers

Personalised Health Care

DNA-based tests and counselling

Personalised Nutrition?
(Personalised Dietary and Phenotype analysis)
Nutrigenetics

Modified from S Massart

Specific groups
or
Individual, Personal, Patterns of Response?

Nutrigenomics

Modified from S Massart


Scientific Background

- Nutritional environment modifies the expression of genes: Which biomarkers?

- Nutrients metabolism is dependent on genetics and this may impact health

- Single gene-related diseases are rare but have a clear impact

- Multiple gene-related diseases are the most frequent and much more complex to analyze: Which impact?
A representative example of modern Nutrigenomics

- **Diet-driven changes:**

  Anti-inflammatory diet mix in healthy but overweight men:

  The effects are personal and can be revealed by a visualisation method (« health Space »)

  Three patterns of changes, in three different group of individuals:

  - Metabolic and oxydative response
  - Metabolic and oxydative with low inflammatory response
  - Inflammation markers

  Bakker et al Am J Clin Nutr 2010; 91 (4) 1044-1059
Dietary advice based on genetics

The "vision"

Blood sample → Genome analysis → Bioinformatics Risk assessment → Dietary advice

Only 24,000 genes...However, 9,000,000 variants

- Single Nucleotide Polymorphisms (SNP)
- Sequencing
**Nutrigenetics today**

**Genome sequencing, SNPs analyses**

- Only coding regions (sequencing)

- 20-50 genes: NAT2, MTHFR, T2R, AMY1, G Proteins
  
  - Weight Management,
  - Heart health,
  - Nutritional needs,
  - Bone health

**Simple paradigm:**

- **MTHFR** → **Mutation** *(C677T)* → **Folate complement**

- **GSTM1** → **Mutation** → **Antioxydant complement**

S Massart
Personalised Nutrition Testing now offered by companies

Examples:

- Sciona
- Genelex
- Market Amerika
- SuraCell

Test pricing: 100 to 1000 US$
Insulin Resistance

• “Analyzes five of your genes that may play an important role in determining how your body manages overall insulin resistance”

• “...assesses five key diet and lifestyle action areas”

<table>
<thead>
<tr>
<th>Gene Analyzed</th>
<th>Role of the Gene in Insulin Resistance</th>
<th>Genetic Variation Screened For Variations Found in Your Gene</th>
<th>Percentage of Population with this Gene Variation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>VDR</td>
<td>Mechanism of Insulin Secretion</td>
<td>CTaqI T</td>
<td>70.6</td>
</tr>
<tr>
<td>VDR</td>
<td></td>
<td>TBsm1C</td>
<td>69.6</td>
</tr>
<tr>
<td>IL-6</td>
<td>Inflammatory Response; Response of Cells to Insulin</td>
<td>G(-174)C</td>
<td>36.3</td>
</tr>
<tr>
<td>TNF-α</td>
<td></td>
<td>G(-308)A</td>
<td>16.5</td>
</tr>
<tr>
<td>PPARγ</td>
<td>Glucose and Lipid Metabolism</td>
<td>Pro12A</td>
<td>61.0</td>
</tr>
<tr>
<td>ACE</td>
<td>Blood Pressure Regulation</td>
<td>II/DD</td>
<td>10.3</td>
</tr>
</tbody>
</table>

*The population frequencies given are normalized for the U.S. population data from the U.S. 2002 Census Report. Population frequencies can vary for different ethnic groups, so for more detailed information, please turn to the Population Frequency Data Table in the Reference Section of your report.
- Not a simple paradigm!!

- Technology:
  - Studying 20 genes = <0.003 % of the genome
  - Studying 1M mutations (Microarray) = 0.03 % of the genome

S Massart
10-30 million SNPs believed to exist (4 million known)

How useful is data on 1 SNP?

The future relies on Genome Wide Association Studies (GWAS) (+100,000 SNPs)
The number of copies of the 16p11.2 region predicts BMI

Mirror extreme BMI phenotypes associated with gene dosage (Genome Wide Association Study (GWAS))

**Deletion**  
Hemizygosity (600 Kb region)

**Duplication**

Relative risk: 43 fold

Number of patients: 95,000

Food intake control

Underweight

Obesity

8.3 (23.2 Males)  
(4.7 Females)

S Jacquemont et al Nature 2011
Contrasting phenotypes

- **autism**: deletion
- **sociability**: normal dosage
- **schizophrenia**: duplication
Understanding also relies on plenty of genomic variations, including:

- Non coding DNA
- Epigenome
- Metagenome

Genome Sequencing will be a key technology to reveal those variants:
DNA sequencing is now amenable to a diagnostic test context

**Cost per human genome ($M)**

- Human Genome Project: 13 years, M$ 3,000

**Time per Human Genome**

- Next Generation Sequencing: Around 1000 US$ 1-2 weeks

**Key issue: Integration of data, bioinformatics**
The real impact of genetic testing?

- **The Case against:**
  - What does it mean to test for one gene polymorphism?
  - Even in studies based on GWAS or deep sequencing the relative risk which is evidenced is very low: around 2-3 fold

- **The Case for:**
  - Well targeted single genetic trait may have a profound impact: ex: cholesterol levels
  - With the advent of whole genome sequencing and progress in bioinformatics, combination of several polymorphism may lead to significant risk factors identification
Potential Benefits

- **At the population level**
  Identify subgroups who might be particularly responsive or resistant to dietary intervention
  Provide a better understanding of the mechanisms involved in disease susceptibility

- **At the individual level**
  Increase awareness of risk
  Motivate behavior changes (diet, lifestyle)
  Enhance prevention
Limitations (1)

- **Technological:** Bioinformatics
  Interpretation of data: Misleading claims

- **Psychological impact** (individual and family)

- **Medical:** Attention drawn away from other modifiable risk factors, decreased use of other services, false sense of security
Limitations (2)

Public Health:
Increased costs associated with personalized diets and designer foods

Targeting vulnerable populations

Concerns surrounding confidentiality, insurance

Dilute or contradict public health messages
“Buyer Beware”

A recent report by the Government Accountability Office highlighted a few of the concerns with four examples of DTC nutrigenomic tests.

- The GAO report raised concerns that the tests may mislead consumers by making unsound and ambiguous predictions about health risks.

- In addition, the test results frequently include recommendations for the consumer to purchase dietary supplements that may be significantly overpriced compared with similar products available through a supermarket or pharmacy and that may, in fact, be harmful for some individuals.
USA: FDA implication

- Direct to consumer (DTC) genetic testing remains as a business model
  - Some bodies have issued statements against DTC genetic model
    - Failure of interpretation, incorrect decision-making
  - Others have championed DTC genetic testing model
    - Personal empowerment, proactive health strategies
  - Others request appropriate oversight for DTC genetic testing
    - Protect individuals from incorrect information, protect privacy
- FDA working with companies to come into compliance with FDA regulations for medical devices
- Panel intended to gain broad-based information on important issues in DTC genetic testing
Nutrigenomics

Specific groups
or
Individual, Personal, patterns of response?

Epigenetics

Nutrigenetics

Modified from S Massart
Long term effects

Ageing

Sexual dimorphism

Epigenetics
If DNA is the **hardware**, epigenetics is the **software** that tells genes what to do.

**Genetics**
- DNA sequence
- Variations
- Irreversible

**Epigenetics**
- Post translational modifications
- Reversible

**Transcription** (expression)
- Replication
- Condensation
- X Inactivation
- Genomic imprinting
- Ageing
- etc...

**C Junien**

The **reversibility** of altered states of chromatin is essential for interactions with the environment.
An on-going construction

The actors: codes, marks and transcription factors accessibility

- Code DNA
- Methylation (CH3)
- Histones
- Variants + modifications

9 classes of marks
≥ 50 activating/repressive marks (sites)

- Folate
- CpG, non-CpG, OHmC
- 5 AzaC

- Flexible!
- But heritable
- Thru cell division

- Caloric restriction
- Stress
- Resveratrol

Silencing of gene expression

- Chromatin Remodeling

- Corepressors/coactivators

- Tissue, stage-specific expression of genes

- Fibers/SCFA, butyrate/sulphoraphane
- Valproate, Trichostatine A (TSA)

C Junien
The Metabolome interactions


Humans: > 500 functionally distinct NORMAL cell types/ca. 10 trillion parenchymal cells
THE “METABOLOME-WIDE ASSOCIATION STUDY” (MWAS) CONCEPT

“The broad non-selective analysis and statistical interrogation of metabolic phenotypes in relation to epidemiologic end-points and risk factors to generate testable physiological or pathway hypotheses”.

Nutrigenomics

Intestinal Metagenomics

Genomics

Epigenetics

Nutrigenetics

Modified from S Massart
The Interface between our two genomes:
A novel paradigm for nutrition

The Human Genome
(23000 genes)

The Intestinal Microbiota
(10 times the number of host cells)
(More than 150 fold increased genetic complexity)

Food
Diet

Health
The human intestinal microbiota: dense, structurally and functionally diverse

- faecal microbiota: 100 trillions microorganisms
- hundreds of species...
- normal consortium adapted and functionally stable
- nutrition, physiology, immunity & protection

Health <-> Disease
Quantitative metagenomics

Sample collecting & processing → High throughput Sequencing → Reference sequence matching → Gene counting → Biological exploration → Diagnostic

30 to 50 millions short sequences → Mapping short sequences and counting genes

Gene abundance profiles
Different for each individual

Reference gene catalog
One for all humanity

Stool sample

Metabolism reconstruction
Ecosystem reconstruction
Genetic variability

A powerful microscope!

H Blottière
Human intestinal microbial genes are largely shared in the cohort

Each individual has
~540,000 of the 3.3 million genes

40% of an individual’s genes are shared with at least 50% of individuals of the cohort

Rare genes = genes shared by less than 20% of individuals = 2.4 million genes

We are all rather similar!

But not identical!!
Enterotypes of the human gut microbiome

Manimozhiyan Arumugam1,2, Jeroen Raes3,4,5, Eric Pelletier3,4,5, Denis Le Paslier3,4,5, Takuiji Yamada6, Daniel R. Mende3, Gabriel R. Fernandes1,6, Julien Tap3,7, Thomas Bruls3,4,5, Jean-Michel Bato7, Marcelo Bertalan8, Natalia Borruel9, Francesc Casellas9, Leyden Fernandez2, Laurent Gautier6, Torben Hansen1,12, Masahira Hattori13, Tetsuya Hayashit14, Michiel Kleerebezem15, Ken Kurokawa15, Marion Leclerc2, Florence Levenez2, Chayovana Manichanh9, H. Bjorn Nielsen9, Trine Nielsen13, Nicolas Pons7, Julie Poullain9, Junjie Qin8, Thomas Sicheritz-Ponten8,19, Sebastian Tims15, David Torrents10,19, Edgardo Ugarte2, Erwin G. Zoetendal15, Jun Wang9,15, Francisco Guarner2, Olaf Pedersen11,13,22,23, Willem M. de Vos2,24, Soren Brunak9, Joel Dore2, MetaHIT Consortium†, Jean Weissenbach9,49,4, S. Dusko Ehrlich2 & Peer Bork1,20.

Europeans, Americans, Asians.
n=33; Sanger

Danes
n=85; Illumina

US
n=154; 454

May 2011
Enterotypes can be viewed as “blood groups” but the reasons for their existence remains to be elucidated. Recent publication: online September 1st (Wu et al, Science)

“Linking Long-Term Dietary Patterns with Gut Microbial Enterotypes”

*Bacteroides* enterotype → protein and animal fat ?

*Prevotella* enterotype → carbohydrate ?

Not modified by short term (10 days) diet intervention

(2 enterotypes found, based on 16S rDNA only – inadequate resolution ?)

They should allow patient stratification & aid to develop personalized medicine and nutrition

H Blottiere
Suggested that Obese Individuals may have a lower Bacteroidetes: Firmicutes ratio than Lean Individuals – and this can be modulated by diet.
Modern ‘non-infectious’ human diseases with associated gut microbiotal disorders.

**Gastric ulcers** (*Helicobacter pylori*)

**Colon and other cancers**

**Autoimmune (AI) diseases**
- Inflammatory bowel diseases- Ulcerative Colitis & Crohn’s (type IV)
- Type 1 diabetes (type IV)- may be prevented by gut bugs and parasites
- Primary biliary cirrhosis
- Celiac disease (type IV hypersensitivity)
- others too?

**Insulin resistance related conditions**
- Type 2 diabetes and obesity...

**Allergies & related immune disorders**
- Asthma, Eczema, Psoriasis......(others?)

**Neuropsychiatric disorders?**
- Autism (?), Schizophrenia?.......(others?)

**Hypertension**....

From: J Nicholson
Inter- and Multidisciplinarity

Handling of data: knowledge management
Bioinformatics, Systems Biology
« Big Science » and « curiosity-driven » science

Information Technology For Health
« services »
Business model

Nutrigenomics
nutrigenetics

Public health Ethics

Technologies: « omics »
- Sequencing
- Epigenetic analysis
- Proteomics
- Metabonomics

Cohorts
Clinical studies (Interventional)
Evidence based

Research Consortia And Networks
The European Nutrigenomics Organisation: linking genomics, nutrition and health research (NuGO)
Challenges of molecular nutrition research: the nutritional phenotype database to store, share and evaluate nutritional systems biology studies

Ben Omnen et al.

Time-Resolved and Tissue-Specific Systems Analysis of the pathogenesis of Insulin Resistance

Robert Kleemann et al.
Nutritigenomics and Nutrigenetics

A real and most important case for the future of Personalised Health Care

Questions and Challenges

☐ Evidence based? To be substantiated

☐ Mechanisms?

☐ Which impact?:
  - group of individuals?
  - individuals?

  - novel biomarkers?

  - novel scientific model:
    integration of data
    multidisciplinarity