IT’S NOT YOUR GRANDMOTHER’S COOKBOOK ANYMORE!
The Chemicals and Genes in Your Food and The Chemicals and Genes in You

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Epigenetics Defined

- Epigenetics refers to the alteration of gene expression, due to a variety of environmental and lifestyle-related factors. Changes do not alter the DNA sequence, but rather how the genes are expressed.
- “Above genetics” or “soft inheritance”¹
- Alterations of genetic material that do not affect the DNA sequence itself, i.e., DNA methylation patterns, chromatin structure, and histone codes, as well as non-coding small RNAs.¹


The behavior of a person's genes doesn't just depend on the DNA sequence - it's also affected by epigenetic factors. Such alterations are caused by lifestyle choices and the environment. Changes in these factors can play a critical role in health and disease.
GENE AND EPIGENETICS

- Genes are the blueprints to the body
- Epigenetics systems can either adapt to keep good genes running and suppress bad genes; or sometimes can be the cause of serious illnesses
- Epigenetic changes can be heritable during cell division
- Expression of genes is regulated by a variety of environmental factors

http://learn.genetics.utah.edu/content/epigenetics/inheritance/
NUTRIGENOMICS DEFINED

- The study of interactions between the various nutrients and phytochemicals contained in food and our genes.

- Through nutrigenomics we can observe how a particular type of diet can influence gene expression and consequently affect the susceptibility of the organism against various diseases and disorders.
# How Diet Affects Our Body

<table>
<thead>
<tr>
<th>Bioactive compound/food ingredient</th>
<th>Food/beverage</th>
<th>Expected effect/target illness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anthocyanins C3G and cyanidin Cy</td>
<td>Fruits, vegetables, red wine</td>
<td>Regulation of adipocyte function</td>
</tr>
<tr>
<td>Epicatechin</td>
<td>Cocoa</td>
<td>Prevention of the oxidative DNA damage, reduction of inflammatory response</td>
</tr>
<tr>
<td>Epigallocatechin-3 gallate</td>
<td>Green tea</td>
<td>Chemopreventive agent in cancer</td>
</tr>
<tr>
<td>Omega-3 fatty acid</td>
<td>Fish oil</td>
<td>Chemopreventive agent in cancer</td>
</tr>
<tr>
<td>Genistein</td>
<td>Soybean</td>
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</tr>
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TRANSGENERATIONAL EFFECTS TESTED ON MICE, APPLICABLE TO HUMANS

- Late gestational high fat diet induces increased risk of metabolic syndrome in the progeny

- This is coupled with hypoadiponectinemia as well as with leptin resistance, and concomitant presence of selective tissue-based epigenetic changes among adipocytokine genes. **Low adiponectin induces metabolic syndrome.**

- Low nutrition in early gestation increases risk of metabolic syndrome later in life
**Transgenerational Effects**

**Glucose in Mice**

**Question to ponder:** Does neonatal catch-up growth induce diabetes in offspring and grand-offspring of affected individuals?

- Male offspring mice and their male grand-offspring not overfed during lactation were observed and compared to the original group of mice that were overfed during lactation.
- Male offspring developed fed and fasting hyperinsulimemia, hypertryglyceridemia, insulin resistance, and glucose intolerance, but not obesity, by 4 months.
- Grand offspring developed fasting hyperglycemia and glucose intolerance by 4 months.

**Conclusion:** Nutritional challenges occurring during sensitive periods of development may have adverse metabolic consequences well beyond the lifespan of affected individuals and manifest in subsequent generations.

Transgenerational progression of metabolic phenotypes through the male lineage supports a potential role for epigenetic mechanisms in mediating these effects. Transgenerational Inheritance of Glucose Intolerance in a Mouse Model of Neonatal Overnutrition.
Transgenerational Effects
Agouti Mouse Studies

- Prenatal exposure to genistein (from soy) leaves a permanent mark on the hematopoietic (formation of blood cellular components) lineage
- Maternal diet during pregnancy results in long-lasting effects on the progeny.
- Supplementation of maternal diet with genistein, a phytoestrogen ubiquitous in the daily diet, altered coat color of agouti mice due to epigenetic changes.

Question to Ponder: Does paternal obesity influence an offspring’s future health status?

- Observed a persistent inverse association between DNA methylation in the offspring and parental obesity.
- At the H19 DMR, no significant associations were detected between methylation patterns and paternal obesity.
- Data suggests an increase in DNA methylation at the IGF2 and H19 DMRs among newborns from obese mothers.
- Hypomethylation at the IGF2 DMR (major fetal insulin-like growth factor) was associated with paternal obesity.

Conclusion: Paternal obesity is associated with IGF2 hypomethylation in newborns.

**Transgenerational Effects - Humans**

**Question to Ponder:** What is the impact of obese parents on their offspring?

- Altered methylation outcomes at multiple imprint regulatory regions found in children born to obese parents, compared to children born to non-obese parents.
- Parental lifestyle or overnutrition influences the reprogramming of imprint marks during gametogenesis.
- The significant and independent association between paternal obesity and the offspring's methylation status suggests the susceptibility of the developing sperm to environmental factors.

**Conclusion:** Newborns of obese parents have altered DNA methylation patterns at imprinted genes. The acquired imprint instability may be carried on to the next generation and increase the risk for chronic diseases in adulthood.
Question to Ponder: What role does the insulin-like growth factor 2/H19 methylation at birth play in determining the risk of overweight and obesity in children?

Conclusion: IGF2 plasticity may be mechanistically important in early childhood overweight or obese status. Findings suggest aberrant DNA methylation at sequences regulating imprinted genes may be useful identifiers of children at risk for early obesity. Children who were overweight or obese at age one year had higher methylation percentages at the H19 DMR at birth compared with those who were neither overweight nor obese.
TRANSGENERATIONAL EFFECTS- NON HUMAN PRIMATES

Question to Ponder: What effect does maternal diet have on an offspring?

- Almost 1/3 of children between 6 and 19 years of age are overweight, and 12% of infants are considered overweight
- Only a portion of the adult female monkeys chronically consuming the HFD became obese and insulin resistant
- All fetal offspring of HFD mothers (O-HFD animals) examined during the early third trimester showed signs of NAFLD, including hepatic inflammation, oxidative stress and/or damage, TG accumulation, and premature gluconeogenic gene activation

Conclusion: Maternal high-fat diet triggers lipotoxicity in the fetal livers of nonhuman primates. The mother does not necessary need to be obese or insulin resistant for the offspring to possess these metabolic diseases

KEY POINTS TO TAKE AWAY

- Certain nutritional exposures may alter the epigenome leading to changes in cell function.
- Gene-specific epigenetic plasticity continues beyond early development and may be lifelong.
- DNA methylation at specific loci is associated with differential disease risk and may be modified by specific nutritional interventions.
- Epigenetic variation is likely (or highly likely) to be an important consideration in developing personalised nutritional recommendations.
Wondering about the baby’s gift of imprinted genes?

I always wanted to have a healthy child?
While genes are inherited from the parents to the offspring, the epigenome is also imprinted. During reproduction and growth, some methylation is replicated on the offspring’s DNA, and some is lost. This creates a unique set of chromosomes and epigenome. Modifications which survive in the offspring are said to be ‘imprinted’.

Disclaimer: Chromosomes aren’t actually methylated like that, the DNA is - this shows inheritance. Chromosomes are also not attached at the centromere until replication, they exist as sister chromatids until then.
NUTRITIONAL EPIGENETICS

Nutrition
Mixture/Extract, Nutraceuticals, Dietary factors, Phytochemicals

Metabolism  Absorption  Gastrointestinal microbiome

Bioavailable Metabolites

Systemic effects
CNS
Neuroendocrine
Immune System

Local effects
Embryo
Organ-Tissue
Somatic Cell
Germ Cell

Changed expression
mRNA, miRNA, ncRNA, protein

Transposon
Genome
(In)stability

Nutritional Epigenomics - Healthy Aging
Reprogramming metabolism, oncogenes, tumor suppressors, oncomiRNAs, tumor suppressor miRNAs
Inflammatory markers, Differentiation markers, Stem cell markers
The Future of Nutrigenomics

- Nutrigenomics has a potential to deliver dynamic biomarkers for nutrition and health status
  - Furnish long-term or static biomarkers for individual disposition towards diet and nutritional imprinting
- Diet = prominent life-long environmental impact on human health
- Nutrigenomics and nutrigenetics are key scientific platforms to promote health and prevent disease through nutrition regarding:
  - Specific health conditions
  - Particular lifestyles
  - Certain stages of life
- Concept of nutrigenomics-rooted personalized nutrition will lead to development of new food products that target individuals and groups of people with similar metabolic phenotypes and genetic risks
- Harmonizing dietary interventions in terms of micro- and macronutrient content and origin

SCOPE OF TRANSGENERATIONAL EFFECTS

- Transgenerational effects do not just apply to food, they can apply to sensory organs as well.
- We all know the phrase “smelling fear”, but turns out, it is REAL.
- Research supports that mice can inherit fear.
- Environmental influences such as stressors, environmental toxicants, etc.

Would you fear this smell?

http://www.soapies-supplies.com/shop/images/P/cherry-almond.jpg
Does transgenerational effects of epigenetics apply to smell?

- Yes!
- Mice trained to fear the smell of a cherry- and almond-scented chemical called acetophenone passed their anxieties onto their pups.
- Compared to control mice, mice born to acetophenone-fearing fathers shuddered more in response to the scent the very first time they smelled it.
- Same applied to a third generation of mice.

Inherited Fears | The Scientist Magazine®
WHAT ABOUT EATING? (EYES BIGGER THAN STOMACH)

http://i1.ytimg.com/vi/dVRhRzE_AkQ/maxresdefault.jpg
SNAKE GENOMICS – burst of gene activity
**Question to Ponder:** Does vitamin D deficiency in childhood obesity lead to reduced insulin sensitivity?

- Higher body mass index (BMI) leads to lower 25(OH)D level
- 25(OH)D deficiency associated with decreased peripheral insulin action
- Cross-sectional study of 64 obese and 32 healthy children aged 6–16 year

**Conclusion:** 25(OH)D deficiency in childhood obesity is associated with enhanced systemic inflammation and reduced insulin sensitivity

*International Journal of Obesity (2014) 38, 46–52; doi:10.1038/ijo.2013.75; published online 18 June 2013*
INSULIN SENSITIVITY AND VITAMIN D

Can we increase insulin sensitivity by increasing the amount of vitamin D intake up a person?

- YES!

- In a randomized control trial conducted by The American Journal of Clinical Nutrition, researchers were able to improve insulin sensitivity in obese adolescents by correcting vitamin D insufficiency.

Am J Clin Nutr April 2013 vol. 97 no. 4 774-781

Swedish researchers have shown that moderate doses of two widely used antioxidants spur the growth of early lung tumors in mice.

Comparison between mice fed a normal diet and mice fed antioxidants in their diet

Antioxidant fed mice developed increased and more aggressive lung tumors and only lived half as long

Antioxidants reduce reactive oxidative species and DNA damage in the cell, however, it also turns down the p53 gene which is crucial to keeping cell growth in check and is often inactivated in cancer

[1] http://stm.sciencemag.org/content/6/221/221ra15.abstract
**Benefits**
- Neutralize free radicals, which damage cells
- Protect cells, DNA, and other organelles
- The body synthesizes some antioxidants
- Used in metabolism
- Vitamins are necessary dietary components

**Where’s the Balance?**

**Risks**
- Free radicals regulate programmed cell death (causes lack of regulation)
- Some can become pro-oxidative at high doses
- Too low of a dose causes deficiency
- Can alter the metabolism of other nutrients and drugs
- Have been shown (in human cohorts) to increase all cause mortality
- Increased cell proliferation is non-specific, fixes damaged cancer DNA
- Down regulate P53, a gene that suppresses tumor growth

Some free radicals are necessary to establish mitochondrial metabolism and physical exercise conditioning.

**Antioxidant Effects**

**Why is this important?**

1. Nutrigenomics builds on the three omics disciplines *transcriptomics, proteomics* and *metabolomics*. Prerequisite for nutritional systems biology, particularly the understanding of the interaction between food components and diet with cells, organs and the whole body.

1. Nutrigenetics and nutrigenomics build the science foundation for understanding human variability in preferences, requirements and responses to diet, and may become the future tools for consumer assessment motivated by personalized nutritional counseling for health maintenance and disease prevention.

**Nutritional Obstacles**
Mitigating effect on offspring even with preprogrammed effect?
Cheap food; sustainable agriculture
Yield vs environment vs diet (plant vs animal)
Lack of scientific knowledge on behavioral sciences to cause people to change
School lunch programs
Traditions - don’t want to give up ice cream
Fast Food; quality food, tasty food
Exercise vs sedentary
Sedentary society
Diets high in meat, eggs and dairy could be as harmful to health as smoking

**Scientific and Medical Problems**
Emerging diseases e.g. obesity, type 2 diabetes
Changing technology and methods
New findings
Environmental factors
Aging
Lack of understanding
Alzheimers disease
Agricultural technology- cheap food, good tasting

**Cultural Problems**
Diet and lifestyle factors
Denial
Habits
Politics
Cultural and ethnic foods
Education
Folklore
‘Outliers’ - villagers with low incidence of heart disease

**Environmental Problems**
School lunch programs
ALL FOR ONE, OR, NONE FOR ALL

- General nutrition guidelines may become a thing of the past
- Personalized nutrition plans are ideal because of:
  - Different methylation of DNA
  - Transgenerational effects stemming from nutrition and the environment

WHAT’S BEST FOR YOU MAY NOT BE WHAT IS BEST FOR OTHERS

Is this our future?