Nutrigenetics and Nutrigenomics: Overview

Martin Kohlmeier, MD, PhD
University of North Carolina at Chapel Hill
Department of Nutrition
and
UNC Nutrition Research Institute
mkohlmeier@unc.edu
Outline

Defining nutrigenetics and nutrigenomics

NGx has a long history

Responders vs. non-responders

The evolutionary history of our genetic blueprint

Why we need to know about NGx in research

What our genetic differences mean

Practical applications
Scope of nutrigenomics
Nutrigenomics is not new

**QUOD ALI CIBUS EST ALIIS FUAT ACRE VENENUM**

Titus Carus Lucretius, around 60 BC

Even those idiosyncrasies with regard to drugs and articles of food which are summed up in the proverbial saying that what is one man’s meat is another man’s poison presumably have a chemical basis.

Archibald Garrod, Croonian Lecture, Royal College of Physicians, 1908
<table>
<thead>
<tr>
<th>Year</th>
<th>Author(s)</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1908</td>
<td>Garrod</td>
<td>Inborn Errors of Metabolism (IEM): cystinuria</td>
</tr>
<tr>
<td>1934</td>
<td>Følling</td>
<td>Discovery of phenylketonuria (PKU)</td>
</tr>
<tr>
<td>1953</td>
<td>Bickel</td>
<td>Effective dietary therapy of PKU</td>
</tr>
<tr>
<td>1994</td>
<td>Calonge et al.</td>
<td>Gene responsible for cystinuria located</td>
</tr>
<tr>
<td>2003</td>
<td>HGP, Venter</td>
<td>Human genome sequence decoded</td>
</tr>
<tr>
<td>2015</td>
<td>23andMe</td>
<td>1 million customers genotyped</td>
</tr>
<tr>
<td>2016</td>
<td>VeritasGenetics</td>
<td>$1000 personal genome sequence</td>
</tr>
<tr>
<td>1942</td>
<td>Waddington</td>
<td>Epigenetics: genetic effects on development</td>
</tr>
<tr>
<td>1975</td>
<td>Riggs, Holliday</td>
<td>DNA methylation sets epigenetic markers</td>
</tr>
<tr>
<td>2006</td>
<td>Waterland</td>
<td>Maternal feeding alters fetal Agouti gene</td>
</tr>
</tbody>
</table>
We are all different
Carrots or Broccoli?

We are all different
Responders vs. Non-responders

How much lactose can I tolerate?

11-12 g lactose in a 240 ml glass of milk
Frequencies of LP in the Old World

Itan et al., 2010
Humans have inhabited diverse ‘nutritopes’ throughout history and have adapted to new food patterns. Small changes in the lactase gene of these people sustain enzyme expression into adulthood. This adaptation helped them to consume lots of milk and survive in environments with otherwise sparse food supplies.
Lactase persistence

Why you want to know about this:
Lactose intolerance often mimics the symptoms of inflammatory bowel disease. You can use predictive genetic assessment to improve dietary guidance.

The normal state (65-70% world-wide) is loss of lactase expression after infancy.

Pastoral populations have evolved variants in the upstream enhancer region causing persistent expression in adulthood.

The persistence alleles are dominant
-13838 A in some Tibetans
-13907 G in about 5% of East Africans
-13910 T in more than 80% of Europeans
-13915 G in many Yemenis, Saudis, Kuwaitis
-13937 A in Xhosa, Brazilians
-13965 G in East Africans
-14009 G in Somalis
-14010 C in Kenyans, Tanzanians
-14042 G, -14107 A in East Africans
Lactase persistence

Labrie et al., 2016
Lactase persistence

Genotype-specific decline of jejunal lactase expression with age is related to the progressive accumulation of epigenetic changes.

Labrie et al., 2016
Genotype-specific decline of jejunal lactase expression with age is related to the progressive accumulation of epigenetic changes.

Advancement of the epigenetic clock appears to depend on the genetic landscape.

Labrie et al., 2016
Persistence (LP) decreases abundance of *Bifidobacteria* and *Lactobacilli* in the small intestine

Szilagyi et al., 2010
Persistence-linked LCT allele -13910 T decreases abundance of the *Bifidobacterium* genus in the small intestine

Goodrich JK et al., 2016
Lactase persistence

Intolerance associated with metabolite profile in vitro

He T et al., 2006
Lactase is the only enzyme in the small intestine that cleaves glucosides of flavonoids and other common phytochemicals, some of which are highly toxic.

Day AJ et al., 2003
Why we need to know about NGx in research
The need to know about NGx

It may be a matter of life and death for some

H1/H1 frequency 1 in 6

Zillikens MC et al., 2009
The need to know about NGx

MTHFR-related blood pressure differences

Wilson CP et al., 2012
The need to know about NGx

16-week riboflavin supplementation lowered BP

RCT in Ireland of treated hypertensive adults with MTHFR TT, achieving an average reduction of systolic BP by 5.6 mm Hg

Wilson CP et al., 2013
The need to know about NGx

Lung embolism

5 per 100,000 of people in their fifties die from lung embolism

3-5% of Americans have a thrombophilic mutation such as factor V Leiden or prothrombin 20210A that increase risk.

Risk of deep vein thrombosis and lung embolism can be reduced with anticoagulant treatment, but most of those at high risk do not know.
The need to know about NGx

Lung embolism

The Women’s Health Initiative randomized 39,876 women to 300 IU vitamin E/day or placebo for about 10 years.

Risk reduction for women with a F5 or F2 mutation was 49% (p=0.014).

What should the treatment of choice be for an incidental asymptomatic finding?

Vitamin E (49% risk reduction), or anticoagulant (>70% RR, risk of bleeding)

Glynn RJ et al., 2007
The need to know about NGx

The response to carbohydrate is genotype-specific

Smith CE et al., 2008
The sucrose (SI) variant rs9290264 is associated with inefficient hydrolysis of sucrose (\(O-\alpha-D\)-glucopyranosyl-(1→2)-\(\beta\)-D-fructofuranoside). Carriers with high sugar consumption have increased stool frequency and have higher risk of irritable bowel syndrome (IBS).

**The capacity to digest sugars differs between individuals**

Henström et al., 2016

---

**Association of the 15Phe variant with IBS**

<table>
<thead>
<tr>
<th></th>
<th>CTRL AF</th>
<th>IBS AF</th>
<th>p Value</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case-control</td>
<td>0.264</td>
<td>0.306</td>
<td>0.0030*</td>
<td>1.26</td>
</tr>
<tr>
<td>PopCol</td>
<td>0.29</td>
<td>0.417</td>
<td>0.045</td>
<td>1.89</td>
</tr>
<tr>
<td>Combined</td>
<td>0.268</td>
<td>0.309</td>
<td>0.0013*</td>
<td>1.27</td>
</tr>
</tbody>
</table>
NGx Studies
Integration of research data

- SNP
- CNV
- LOH
- Genomic rearrangement
- Rare variant
- DNA methylation
- Histone modification
- Chromatin accessibility
- TF binding
- miRNA
- Gene expression
- Alternative splicing
- Long non-coding RNA
- Small RNA
- Protein expression
- Post-translational modification
- Cytokine array
- Metabolite profiling in serum, plasma, urine, CSF, etc.

Genome
- DNA
- TFbs
- Me
- Histone
- Transcription

Epigenome
- Gene
- Alternative splicing
- miRNA

Transcriptome
- mRNA

Proteome
- Protein

Metabolome
- Metabolites

Phenome
- Cancer
- Metabolic syndrome
- Psychiatric disease

Nature Reviews | Genetics 2015
Practical Applications
Practical applications

Personalized Online Nutrition Guidance

Gluten-free
Lactose-free
Genotype-specific

Vegetarian
Vegan
Low-Carb
Practical applications

Product development

- Smart Balance Lactose-Free Fat Free Milk and Omega3s
- Lactaid Lowfat Milk
- Breyers All Natural Ice Cream - Lactose Free
- Yoplait Lactose Free Greek Yogurt
- Yoplait Lactose Free Regular Yogurt
Practical applications

Regulations and policies

Should high-dosed folate require a prescription?

How much should the caffeine content be allowed to vary between brews?

Should these fava beans come with a safety warning?
Final comments

Intervention effects in genetic subgroups are easily obscured by the lack of significant response of the majority.

Some nutritional interventions are only effective, if they are targeted to genetically susceptible models or individuals.

The likely effect size of some genotype-specific interventions is as large as that of medical treatments.
Questions?