Application of Nutrigenomics Toward Personalized Dietary Recommendations

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How can genetic variation influence response to diet?

How can “omic” approaches be incorporated into the study of gene-diet interactions?

*How do we move forward to personalized dietary recommendations, now and in the future?*
Nutrigenomics:
Study of the interactions between genes and diet.
Study of how genetic variation influences response to diet.

- GENOME
- EPIGENOME
- MICROBIOME
  Gut bacterial genome

Health & Disease Risk
**Nutrigenomic Approaches: Analysis of Gene-Diet Interactions**

- **Transcription**
  - DNA → mRNA
- **Translation**
  - mRNA → Protein

**Protein Function**
- e.g., enzyme activity

**Susceptibility**
- (e.g., genetic variation)

**Down-stream Effects**

**Epi/genomics**

**Transcriptomics**

**Proteomics**

**Metabolomics**

**Participants**

5 10 15 20 25 30 35

- a.
- b.
- c.
The human diet is complex.

- 1000s of compounds
- Variety of methods of food preparation
  - Structure and particle size
  - Bioavailability to host
How can genetic variation influence response to diet?

- Food preference
- Food tolerance
- Absorption
- Transport
- Metabolism
- Effect in target tissue

Lampe and Potter, in Gene-Environment Interactions (Costa and Eaton, eds), 2006
Metabolism: NAT2 Polymorphism Modifies Dietary-Induced DNA Damage in Colorectal Mucosa

- 2-day vegetarian diet vs 2-day grilled meat diet
- Measured DNA strand breaks in epithelial cells extracted from stool samples

Increased Urinary Mutagenicity with Fried Red Meat Intake in Individuals with UGT1A1*28

2-week controlled feeding study in 60 subjects
Fed red meat cooked at 250°C
Mutagenicity of urine tested using Salmonella YG1024 (+S9)

<table>
<thead>
<tr>
<th>UGT1A1 genotype</th>
<th>Point estimate</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/6</td>
<td>747</td>
<td>-1166-2660</td>
<td>0.450</td>
</tr>
<tr>
<td>6/7 or 7/7</td>
<td>4062</td>
<td>1623-6511</td>
<td>0.003</td>
</tr>
</tbody>
</table>

P for interaction between UGT1A1 and meat intake = 0.04

Metabolism of Chemopreventive Phytochemicals: Isothiocyanates Conjugated by Glutathione S-Transferases and Excreted in Urine

GST

\[ \text{ITC} + \text{GSH} \rightarrow \text{ITC-glutathione} \]

\[ \gamma\text{-GT} \]

\[ \text{ITC-glutathione} \rightarrow \text{ITC-cysteine-glutathione} \]

\[ \text{CG} \]

\[ \text{ITC-cysteine-glutathione} \rightarrow \text{ITC-cysteine-cysteine} \]

\[ \text{AT} \]

\[ \text{ITC-cysteine-cysteine} \rightarrow \text{ITC-N-acetylcysteine} \]

Dithiocarbamates, excreted in urine
GSTM1-null subjects had:

- Greater rate of urinary excretion of sulforaphane in first 6 h
- Higher % sulforaphane excretion over 24 h

Integrating Genomics and Metabolomics: A Cross-Sectional Study

- 284 men
- GWA study data with serum metabolomics-based quantitation of 363 metabolites.
- Reported associations of frequent SNP with differences in the metabolic homoeostasis, explaining up to 12% of observed variance.

Genotypes and Metabotypes: Endogenous Metabolite-SNP Interactions

- Associations of frequent SNP with differences in the metabolic homoeostasis explained up to 12% of observed variance.
- Using ratios of certain metabolite concentrations as proxy for enzymatic activity, explained up to 28% of the variance (P-values $10^{-16}$–$10^{-21}$).
- Identified 4 variants in genes coding for lipid metabolism enzymes (FADS1, LIPC, SCAD and MCAD), where corresponding metabolic phenotype matched pathways in which these enzymes are active.

Genetically Determined Metabotypes: A GWA study of metabolic traits in human urine

- Designed to investigate the detoxification capacity of human body.
- Tested for associations between 59 metabolites in urine from 862 male participants in the SHIP study and replicated the results in independent samples.
- Reported 5 loci with joint $P$ values of association from $3.2 \times 10^{-19}$ to $2.1 \times 10^{-182}$. Variants at 3 loci previously linked with important clinical outcomes: $SLC7A9$ is a risk locus for chronic kidney disease, $NAT2$ for coronary artery disease and genotype...

Gut microbial variation:
Metabolism of soy isoflavone daidzein

Daidzein → Dihydrodaidzein → Cis/Trans-isoflavon-4-ol → O-Desmethylandolensin → Equol

Urinary Equol Excretion

30-50% of individuals produce

1 nmol/d - 100 nmol/d - 1000 nmol/d - 10000 nmol/d
**INTERVENTION:** Lymphocyte Gene Expression Differentially Induced in Equol-Producing and Nonproducing Women

- 30 postmenopausal women
- ~900 mg isoflavones for 84 d
- Gene expression array of peripheral lymphocytes
- 27 genes changed with isoflavones
- Stronger effect on estrogen-responsive genes in equol producers than nonproducers.

Gut Microbiome Phenotypes: Enterotypes

Focusing efforts in areas where evidence is suggestive, but inconclusive, most likely to result in findings that can advance scientific knowledge or change public health practice

- Understand the mechanisms
- Reconcile the heterogeneity

Application of genomic and systems approaches to understand:

- Biologic pathways and mechanisms
- Complexity of effects of dietary patterns
- Behavior
Ultimate Goal of Metabotyping

• Develop a novel approach to personalized health care based on a combination of genotyping and metabolic characterization.
• Identify genetically determined metabotypes that can subscribe the risk for a certain medical phenotype, the response to a given drug treatment, or the reaction to a nutritional intervention or environmental challenge.
• Characterize microbial modification of effects of diet.

What do we need to get there?

- Sufficiently sensitive technologies to detect small, but physiologically relevant, differences or changes in response to diet.
- Data analysis, visualization, and annotation methods.
- Ability to integrate the various omics platforms in a systematic fashion.
- Characterization of phenotypes.
Is there potential for personalized, or more precise, individual dietary recommendations?

- Yes, but still have to:
  - Establish the relevant parameters
  - Integrate the omics data
- Don’t lose sight of the broader public health messages that can have the greatest impact on the largest number of people