Assessing the Health Affects of Bioactive Foods Component: Session 5

Overview of Systems Biology: Sources of Phenotypic Variation

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UC Davis Center of Excellence in Nutritional Genomics
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There are 2 sources of cholesterol: food and family.

You bring 2 things to the dinner table — Your appetite and your genotype.
The source of phenotypic variation is common genetic variation, modified and modulated through epigenetic, environmental, sociocultural and lifestyle filters.
140 years after Mendel described the first heritable phenotype (round \( R \) versus wrinkled \( r \)) researchers isolated the genetic determinant, “starch branching enzyme 1” (SBE1). The \( rr \) genotype results in the accumulation of sucrose in early seed development which causes these seeds to wrinkle when they mature.
Modifying and potentiating filters of genetic variation

It is unlikely that a single gene, SNP, mutation, biomarker or risk factor will have positive predictive value for chronic disease and certain types of cancer.
Diet is a key component of our environment.
# Soy — a model functional food

## DIETARY INPUT
Nutritious foods and food supplements with health promoting bioactive properties

## PROCESS
Molecular mechanism(s) for bioactivity

## OUTCOME
More effective dietary Interventions to optimize health and reduce disease risk

<table>
<thead>
<tr>
<th>Isoflavones (genistein)</th>
<th>Binds hERβ receptor to affect estrogen-dependent gene expression</th>
<th>Mitigate post-menopausal symptoms, reduce cancer risk</th>
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</thead>
<tbody>
<tr>
<td>Protopsins (lunasin)</td>
<td>Induced chemopreventive gene expression</td>
<td>Reduce cancer risk</td>
</tr>
<tr>
<td>Oils (n-3;n6)</td>
<td>Binds GPR40 (7-TMR)</td>
<td>Amplify glucose induced insulin secretion</td>
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</table>
From Hanahan and Weinberg, 2000 Cell 100:50-57
What next?

Individualized nutrition and genome-based dietary recommendations

Roche Holding’s AmpliChip CYP2D6
NitorMed’s BilDil
CYP2C8 Test for granulocytopenia
What this entails?

↓ A multidisciplinary approach to studying diet x gene interactions.

↓ Technology for low-cost, high throughput SNP analysis, sequencing and gene expression profiling.

↓ Access to datasets for large, diverse human populations that include dietary and medical histories, genotype and gene expression data and metabolomic profiles on various bodily fluids.

↓ Access to information from studies on model animal systems.

↓ Bioinformatic tools and theories for dimensionality reduction and visualization of large, complex datasets.

↓ Use of “best practices” for the obtaining, storing, and handling confidential information involving human subjects.

↓ A “systems biology” approach to investigating the relationship between nutrition and disease.
The need for systems biology

All the other genes I don’t know about, I don’t care about

Gene B → Gene A
Gene D → Gene C
Gene E

List of ALL genes
List of metabolites
Biological Processes
Pathways Networks

1990

2005
Systems biology

- transcriptome
- proteome
- genotype
- gene
- gene expression profiling
- metabolome
- informational networks
- Informatics
The need for systems biology: the case for dimensionality reduction

Experiments are designed with the assumption that only a few parameters change from sample to sample.

Caloric Restriction v.s. Control Diet

High Dimensionality

- Informatics
- Expression profile
- Biochemical pathway
- Inflammation
- Oncogene-induced pathway

Tens of thousands of genes are tested on tens and hundreds of samples.

The datasets may be reduced back to a few embedded dimensions responsible for observed changes.
Systems biology involves the representation and analysis of an intact biological system. Like many of the technological developments over the past 20 years, such as genomics, proteomics, combinatorial chemistry, and bioinformatics, there is high hope that systems biology will help move molecular research closer to the practice of medicine. Science traditionally has taken a reductionist approach that evolves to focus on the integration of data from these new technologies, but will this be enough to effect the transition from data to information, to knowledge to biomedical application?

Michael N. Liebman Ph.D. U. Penn
Nutritional genomics is the study of the molecular interactions between nutritional stimuli and the genome, and how these interactions promote health or cause disease in human populations.
Sources of nutrigenomic complexity

- Variety of foods
- Seasonal variations in food selection and content
- Food fads and public response to news, studies and ads
- Food preparation and cooking
- Cultural and religious background
- Socio-economic status, income, geographic environment
- Access to health care
- Age and health status
- Exercise, life-style
- Genetic background
- Complexity of disease
Common genetic variation:
The source of phenotypic variation

Nutritional genomics seeks to link diet and disease risk through common genetic variation in human populations
The case for nutritional genomics.
Newborn Testing.
Since 1962, millions of infants have been screened for IBEMs

- 188 “genetic diseases” (inborn errors of metabolism — IBEM) have been identified.
- Last year, 7 million US newborns were screened for from 4 to 16 IBEMs.
- 3000 infants were diagnosed with serious disorders
- Every state screens for PKU, galactosemia
- Dietary intervention is the preferred treatment for PKU and galactosemia.
The case for nutritional genomics.
What the experts are say.
Prof. Bruce N. Ames, CHORI Director, Pilot Projects Core

“Single nucleotide polymorphisms provide a powerful tool for investigating the role of nutrition in human health and disease and … can contribute to the definition of optimal diets.”

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<tr>
<th>Allele 1</th>
<th>Allele 2</th>
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<tr>
<td>G-C</td>
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</table>
• Human genome consists of 3 billion base pairs

• Humans are 99.9% identical at the DNA level

• 0.1% difference represents ~6 million SNPs

• 150,000 to 300,000 are coding SNPs (cSNPs)

• 1/3 of cSNPs in the enzyme-encoding gene > $K_m$ of the enzyme.

http://snp.cshl.org;
http://snp.ims.u-tokyo.ac.jp
Coding SNPs and the $K_m$ Concept*

SNPs that increase the $K_m$ reduce the enzyme’s affinity for its substrate or cofactors, thus reducing its reaction rate.

“About 50 human genetic disease are the result of defective enzymes that can be remedied or ameliorated by administering high doses of the vitamin component of the corresponding coenzyme.”


http://phillips.mbb.ki.se/frames/structures/ADH2.html
http://nutrigenomics.ucdavis.edu

National Institutes of Health, 3/25/05
## Potential Vitamin Responsive SNPs

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<thead>
<tr>
<th>Enzyme</th>
<th>Cofactor</th>
<th>Δ bp</th>
<th>Δ aa</th>
<th>Freq(%)</th>
<th>$K_m$ *</th>
</tr>
</thead>
<tbody>
<tr>
<td>MTHFR</td>
<td>FAD</td>
<td>677C→T</td>
<td>222A→V</td>
<td>~15</td>
<td>↓</td>
</tr>
<tr>
<td>ALDH</td>
<td>NAD</td>
<td>-</td>
<td>487E→K</td>
<td>~50 †</td>
<td>150 fold ↓</td>
</tr>
<tr>
<td>GPDH</td>
<td>NADP</td>
<td>131C→G</td>
<td>44A→G</td>
<td>11</td>
<td>5 fold ↓ ‡</td>
</tr>
</tbody>
</table>

* Increased $K_m$ for cofactor = decreased affinity
† Asian heterozygote + homozygote
‡ Rural southern India, may be aided by increased intake

http://www.kmmutants.org/
Identification of a variant associated with adult-type hypolactasia

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Adult-type hypolactasia, also known as lactase non-persistence (lactose intolerance), is a common autosomal recessive condition resulting from the physiological decline in activity of the lactase-phlorizin hydrolase (LPH) in intestinal cells after weaning. LPH hydrolyzes lactose into glucose and galactose. Sequence analyses of the coding and promoter regions of LCT, the gene encoding LPH, has revealed no DNA variations correlating with lactase non-persistence\textsuperscript{1,2}. An associated haplotype spanning LCT, as well as a distinct difference in the transcript levels of ‘non-persistence’ and ‘ persistence’ alleles in heterozygotes, suggest that a \textit{cis}-acting element contributes to the lactase non-persistence phenotype\textsuperscript{3,4}. Using linkage disequilibrium (LD) and haplotype analysis of nine extended Finnish families, we restricted the locus to a 47-kb interval on 2q21. Sequence analysis of the complete region and subsequent association analyses revealed that a DNA variant, C/T\textsubscript{13910}, roughly 14 kb upstream from the \textit{LCT} locus, completely associates with biochemically verified lactase non-persistence in Finnish families and a sample set of 236 individuals from four different populations. A second variant, G/A\textsubscript{22018}, 8 kb telomeric to C/T\textsubscript{13910} is also associated with the trait in 229 of 236 cases. Prevalence of the C/T\textsubscript{13910} variant in 1,047 DNA samples is consistent with the reported prevalence of adult-type hypolactasia in four different populations. That the variant (C/T\textsubscript{13910}) occurs in distantly related populations indicates that it is very old.
The frequency of lactose intolerance varies with age, race and ethnicity.

- N. European
- Indian children
- Afr American children
- Indian adults
- Mex American - adult
- Cretans
- Cypriots
- N. American Jews
- Mexicans - rural
- African American - adult
- Alaskan Native
- Asian Americans
- SE Asians

% Intolerance by Population
SNPs reduce transcription of lactase gene

Lactase

MCM6

2q21

If common genetic variants (e.g., SNPs) in genes encoding enzymes (or their promoters), can affect reactions rates in metabolic pathways, then these genetic variation in human populations may explain differences in the way we respond to, and benefit from, our nutritional environment.
Lactose intolerance
Alcohol intolerance
Galactosemia
MTHFR
GPDH
NAT2
PKU

Adverse diet/genome interactions due to well known mutations and common genetic variants are just the tip of the iceberg.
What are some of the other SNPs that may be keeping us from deriving full benefit from our nutrition?

What genetic variants are we carrying in our genome, that over time, and in response to the foods we eat, will increase our risk of disease?

What adjustments can we make in our diets now that will compensate for the diet-related genetic variants so that we can achieve and enjoy optimal health earlier and maintain it longer?