Nutritional Epidemiology in the Genomic Age

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If we could give every individual the right amount of nourishment and exercise, not too little and not too much, we would have found the safest way to health

Hippocrates (460–377 BC)
Father of Western medicine
Nutritional Epidemiology

- Epidemiology – study and analysis of patterns, causes and effects of health and disease conditions in populations

- Role of nutrition in the etiology of disease

- Monitoring of nutritional status of populations

- Develop and evaluate interventions to achieve and maintain healthy eating patterns among populations
Nutritional Epidemiological Studies

- Correlation studies
- Special exposure groups
- Migrant studies
- Case control and cohort studies
- Controlled trials

Willett W. Overview of Nutritional Epidemiology
gDOI:10.1093/acprof:oso/9780199754038.003.0001
Genetics in Nutritional Epidemiology

- Every person is genetically unique
- Assessments of human nutrition are not complete without taking into account the underlying genetic variability
- Frequencies of genetically-determined traits/diseases differ among races and even among ethnic groups of the same race
- Even within populations, risk for chronic disease differs between subgroups because of their genetic makeup
Gene by Environment Interaction

- Genotype by environment interaction results when the same genotype gives rise to two variations in the expression of the same phenotype in two different environments.

- Distinct effects of an environmental factor in individuals with different genotypes or

- Distinct effects of a genotype in two different environments.
Why study gene by environment interactions?

- Better understand disease etiology
- Better assess population disease risk related to genetic and environmental risk factors
- Informs biological pathways
- Can design new preventative and therapeutic strategies
- Offer tailored preventative advice that is based on knowledge of genetic susceptibility
Gene-Nutrient interactions
Model I - Phenylketonuria

Genotype increases the expression of risk factor

High levels of phenylalanine in blood

Mutation in phenylalanine hydroxylase

PKU
Model II – Xeroderma Pigmentosum

Model 2

Genotype excarabates the effect of the risk factor

Risk factor → Genotype → Disease

Mutations in nucleotide excision repair enzymes

UV radiation → Skin cancer

Skin cancer
Model III- Porphyria variegate

- **Model 3**
  - Mutation in PPOX gene
  - The risk factor excarabtes the effect of the genotype
  - Skin problems
  - Barbiturates and seizure medications
  - Disease
  - Genotype
  - Risk factor
Model IV- alpha-1 antitrypsin deficiency

Genotype and risk factor each influence the risk by themselves

Model 4

Mutation in SERPINA1

Lung disease

Smoke or pollutants

Model 4
Model V-G6PD deficiency

Both genotype and risk factor are required to raise the risk

- genotype
- risk factor
- disease

Model 5

Mutation in glucose 6 phosphate dehydrogenase

Hemolytic anemia

Fava bean consumption
Nutrigenetic differences

- Most of them may have been inherited from our ancestors
- Genetic variation affects food tolerances among populations
- Nutritional environments seem to be the major determinants of human variation evolution
- Populations vary in their requirements for foods and response to diet
Uric acid, fructose and genetic variants in different populations
Serum uric acid

Adenosine mono phosphate (AMP) → Xanthine → Uric acid → Allantoin

Guanosine mono phosphate (GMP) → Xanthine → Uric acid

Inosine mono phosphate (IMP) → Xanthine oxidase → Uric acid

Humans and some higher primates: Uricase
Hyperuricemia and disease states

Choudhary et al., Cardiorenal Med. 2013; 3: 208-220
Dietary Factors affecting serum uric acid levels

Fructose
[Carbonated beverages, most canned products, honey]
- ATP depletion
- Competition with uric acid for the same transporter (SLC2A9)

High-purine foods and amino acids
[Organ meats such as liver, spleen, heart etc]
- AMP, GMP or IMP
- Hyperuricemia

Alcohol
- Dehydration

ATP depletion
- Competition with uric acid for the same transporter (SLC2A9)
- Hyperuricemia

AMP, GMP or IMP
- Hyperuricemia
Strong Heart Family study (SHFS) [PI: Dr. Shelley Cole]

- Is a genetic study of CVD risk in American Indians
- It is the genetic component of the Strong Heart Study started in 1998
- More than 3800 members from multigenerational families enrolled from three centers located in Arizona, Dakotas and Oklahoma
Overweight/obese Hispanic children aged 4-19 years were recruited

Some unique phenotypes such as calorimetry measurements, physical activity and energy expenditure have been collected

Genome-wide SNP, exome and metabolomic data available
## Descriptives

<table>
<thead>
<tr>
<th></th>
<th>SHFS</th>
<th>VFS</th>
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<tbody>
<tr>
<td>Age</td>
<td>39.50 ± 17</td>
<td>11.0 ± 4</td>
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<tr>
<td>Serum uric acid (mg/dl)</td>
<td>5.1 ± 1.5</td>
<td>5.2 ± 1.7</td>
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<tr>
<td>Hyperuricemia (%)</td>
<td>17</td>
<td>25</td>
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<tr>
<td>Sugars intake (% of total calories)</td>
<td>16.3</td>
<td>22</td>
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<td>Heritability (%)</td>
<td>46</td>
<td>45</td>
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SNPs associated with serum uric acid concentrations differ across populations

<table>
<thead>
<tr>
<th>SNP</th>
<th>Gene</th>
<th>Hispanics (β)*</th>
<th>American Indians (β)§</th>
<th>African Americans (β)¶</th>
<th>Caucasians (β)¶</th>
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<tbody>
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<td>rs2231142</td>
<td>ABCG2</td>
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<td>rs6449213</td>
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<tr>
<td>rs780094</td>
<td>GCKR</td>
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<tr>
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<td>-0.01</td>
<td>-0.03</td>
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</table>

<table>
<thead>
<tr>
<th>SNP</th>
<th>Gene</th>
<th>Hispanics*</th>
<th>American Indians§</th>
<th>African Americans¶</th>
<th>Caucasians¶</th>
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<tr>
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<td>C (0.14)</td>
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<tr>
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<td>A (0.18)</td>
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<td>T (0.11)</td>
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<tr>
<td>rs11751616</td>
<td>SLC16A9</td>
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<tr>
<td>rs1165205</td>
<td>SLC17A3</td>
<td>T (0.38)</td>
<td>T (0.31)</td>
<td>T (0.13)</td>
<td>T (0.46)</td>
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</table>

Uric acid and Fructose

- Uric acid is a byproduct of fructose degradation and shares a transporter with fructose (GLUT9/SLC2A9)

- Fructokinase is poorly regulated and phosphorylates fructose rapidly

- Fructose upregulates its transporter GLUT5 as well as fructokinase

- Serum uric acid increases rapidly after ingestion of fructose

Fructose interferes with uric acid excretion
Genotype-specific differences in SUA/added sugars

Minor allele shown next to the SNP in parentheses; added sugars are shown as percent of calories.
Genotype- and Ethnic-specific responses of uric acid to fructose challenge
Effect of fructose challenge on serum uric acid levels

<table>
<thead>
<tr>
<th>Prescreening</th>
<th>Study Participants</th>
<th>Nutrient challenge &amp; Timepoints</th>
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<tbody>
<tr>
<td>40 individuals</td>
<td>20 Caucasian Americans</td>
<td>men Fr. challenge – baseline</td>
</tr>
<tr>
<td></td>
<td></td>
<td>women Fr. challenge – 30min</td>
</tr>
<tr>
<td></td>
<td></td>
<td>men Fr. challenge – 1hr</td>
</tr>
<tr>
<td></td>
<td>20 African Americans</td>
<td>men Fr + Cf challenge -3hr</td>
</tr>
<tr>
<td></td>
<td></td>
<td>men Fr + Cf challenge – 24hr</td>
</tr>
</tbody>
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Serum uric acid response to fructose challenge (by Ethnicity and Sex)
Serum uric acid response to fructose challenge (by Ethnicity and Obesity status)
Serum uric acid response to fructose challenge (by Ethnicity and SLC2A9-rs16890979)

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>CC</th>
<th>CT</th>
<th>TT</th>
</tr>
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<tbody>
<tr>
<td>0 min UA (mg/dL)</td>
<td>4</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>30 min UA (mg/dL)</td>
<td>7</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>60 min UA (mg/dL)</td>
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<td>120 min UA (mg/dL)</td>
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<td>180 min UA (mg/dL)</td>
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Serum uric acid response to fructose challenge (by Ethnicity and *ABCG2 - rs2231142*)
Effect of \textit{ABCG2} genotype (rs2231142) on serum uric acid concentrations during a fructose load

Dalbeth et al. Arthritis Research and Therapy. 2014; 16:R34
Serum uric acid response to fructose challenge (by ethnicity and SLC17A1-rs1183201)
Population-specific effects of *SLC17A1* on serum uric acid concentrations during a fructose load

Serum uric acid response to fructose challenge (by ethnicity and genetic risk score)
Individual genetic variation in human populations affects nutrient metabolism

Nutritional epidemiological studies should take into account the individual genetic variation

There is a need to optimize nutrient intake for each individual in the context of genetic diversity and complexity of nutrient metabolism.

There is a need to ensure that nutritional genetic information is used in a socially responsible manner as it relates to various populations.
• UNC NRI faculty and staff

• NIH Grants
  NIH R01 DK092238, NIDDK P01 DK056350

• Participants of all studies

• Collaborators
  Texas Biomedical Research Institute, San Antonio
  Baylor College of Medicine, Houston

• Voruganti Lab