The Role of Host: Genetic Variation

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Dietary Requirements are Complex Traits

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<th>Physiological Processes</th>
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American Society for Nutrition Nutrition Research Priorities

Variability in Responses to Diet & Food
Achieving personalized nutrition with dietary recommendations tailored to each person’s needs.

Healthy Growth, Development and Reproduction
Understanding how nutrition during critical, early periods of development (including pregnancy) impacts future health.

Health Maintenance
Improving health with noncommunicable disease prevention and weight maintenance.

Medical Management
Slowing disease progression through nutrition with improved responses to therapy and survival rates.

Nutrition-Related Behaviors
Understanding how the human brain influences food choice and nutrition-related behaviors.

Food Supply & Environment
Realizing the potential of the food environment to improve diet and lifestyle choices.

Responders vs. Non-responders

Human Genome Project (1990-2003)

- Assemble & understand cellular networks
- Understand the genetic basis of difference in nutrient requirements

http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml
Common variations in DNA sequence
- Contribute to genetic diversity
- Frequency of about 1 in every 1000 bases of DNA
- There are 10 M SNPs in the human genome.

SNPs contribute to complex traits that include susceptibility to chronic diseases, metabolism and drug efficacy.
Human Genetic Variation
Copy Number Variants (CNVs)

- Common variations in gene copy number
- Contribute to genetic diversity
- Result from gene duplication
- Can have functional consequences

CNVs also contribute to complex traits that include metabolism and drug resistance.
The evolution of genes - creation of genetic variation

- Mutation
- Expansion
  - selection
  - drift

Identify genes that evolve rapidly or regionally from selection

comparative genomics
  - within and among species
Human Genetic Variation
Nutrition and Evolution
Selective Sweeps

[Favoured variant]

[Neutral variant]

Selective sweep

Mutation/recombination
Lactose Tolerance was enabled by Genetic Mutation and the Food Environment

BMC Evolutionary Biology 2010, 10:36  https://doi.org/10.1186/1471-2148-10-36

**Phenotype**

Interpolated map of Old World LP phenotype frequencies. Dots represent collection locations. Colours and colour key show the frequencies of the LP phenotype estimated by surface interpolation.

**Genotype**

Predicted Old World LP phenotype frequencies based on LP-associated allele frequencies. LP frequency prediction assumes Hardy-Weinberg equilibrium and dominance. Crosses represent collection locations where all 4 currently known LP-associated alleles were genotyped, and diamonds represent collection locations where the only data on the -13,910 C>T allele is available. Colour key shows the predicted LP phenotype frequencies estimated by surface interpolation.
Genetic Adaptations to Local Environment


https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5154245/
Amylase CNVs expanded in agrarian human populations to improve starch digestion
Diet-related genes that display genomic signatures of adaptive evolution by selection

<table>
<thead>
<tr>
<th>Gene</th>
<th>Species/function</th>
<th>References</th>
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<tr>
<td>HFE</td>
<td>human iron homeostasis</td>
<td>Genetics 2003;165(1):287-97</td>
</tr>
<tr>
<td>PPARα</td>
<td>human nuclear receptor</td>
<td>Genome Res 2002;12(12):1805-14</td>
</tr>
<tr>
<td>CYP1A2</td>
<td>human arylamine metabolism</td>
<td>Am J Hum Genet 2002;71(3):528-42</td>
</tr>
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</table>

Pathways

- Amino acid metabolism: human, chimp  
  Science 2003;302(5652):1960-3
- Amino acid transport: chimp  
  Science 2003;302(5652):1960-3
- Purine metabolism: chimp  
  Science 2003;302(5652):1960-3

Neural Tube Defects

Homocysteine Health Outcomes

Anti-folate Drugs Toxicity/Efficacy

Requirements

Impact of Genetic Variation on Dietary Folate Requirements

Polymorphisms in Folate Encoding Candidate Genes
MTHFR 677C>T and 1298A>C Variants are in Linkage Disequilibrium (LD)

- **Catalytic Domain**
  - Base Pair: 28 167 358 559 677
  - Gene Sequence: GCC
  - Protein Sequence: Ala

- **Regulatory Domain**
  - Base Pair: 1298 1768
  - Gene Sequence: GTC
  - Protein Sequence: Val

**Normal Allele**
- Gene Sequence: GCC
- Protein Sequence: Ala
- Glu

**Variant Allele**
- Gene Sequence: GTC
- Protein Sequence: Val
- Ala

- **Folate**
  - MTHFR 677C>T
  - + Folate: FAD
  - - Folate: FAD
**Benefit and Risks of MTHFR Polymorphism**

**In utero Risk**

“T” allele

- Low folate status
- Higher folate requirement
- Birth defects
- Miscarriage

**Adult Benefit**

“T” allele

- Physician's Health Study – Colon Cancer Risk

![Graph showing cancer risk ratios for different MTHFR genotypes: CC/CT, TT.](Cancer Res. 57: 1098-1102)
Allelic Frequency of the MTHFR 677 C->T Polymorphism

(TT) Frequency

Mexicans 30%
Tuscanian (Italy) 30%
Africans 0%
African Amer 2%
Yemenite Jews 2%
Muslim Arab Israelis 16%
Asians 19%
Caucasians 9%
Percent difference in Hcy and other 1-C markers between MTHFR homozygotes in a non-fortified population

- Large scale study of 10,601 Norweigens (non-fortified population)
- Genotyped for 13 common polymorphisms

Fredriksen et al. 2007. Human mutation 28(9), 856-865
Folate Intake at RDA Levels Is Inadequate for Mexican American Men with the
Methylenetetrahydrofolate Reductase 677TT Genotype¹⁻³

Claudia Solis,⁴ Kristin Veenema,⁴ Alexandre A. Ivanov,⁴ Sally Tran,⁴ Rui Li,⁴ Wei Wang,⁵
David J. Moriarty,⁶ Charles V. Maletz,⁷ and Marie A. Caudill⁸*
MTHFR 677TT Genotype Markedly Affects Biomarkers of Folate Status in Men Consuming the Folate RDA

Folate Treatment with 400 µg DFE/d

Deficient (<6.8 nmol/L)
- 34% TT (10 of 29)
- 16% CC (5 of 31)

Deficient (>14 µmol/L)
- 79% TT (23 of 29 men)
- 7% CC (2 of 31 men)

Solis et al. JN 2008
WHO Guidelines for Prevention of NTDs with Folate Bayesian Model
WHO Guidelines for Prevention of NTDs with Folate Bayesian Model

**Genotype model**
- **Inputs:**
  - North - *MTHFR* distribution observed among participants in folic acid dosing trial
  - South - *MTHFR* distributions reported in literature
- **Output:**
  - Estimated *MTHFR* genotype

**Concentration model**
- **Inputs:**
  - Estimated *MTHFR* genotype
  - Northern or southern residence
  - Reported months consuming 400 µg/day folic acid supplementation before neural tube closure adjusted for compliance
- **Output:**
  - Estimated RBC folate concentration

**Risk model**
- **Inputs:**
  - Estimated RBC folate concentration at neural tube closure
  - Observed neural tube defect outcome
- **Output:**
  - Estimated association between RBC folate concentration and neural tube defect risk
WHO Guidelines for Prevention of NTDs with Folate
Bayesian Model
Food Intolerances
Dietary Requirements
Susceptibility to metabolic disease

Genome Primary Sequence
Genome Programming
Gene Expression

Human Genome
Dietary Components

Food Intolerances
Dietary Requirements
Susceptibility to metabolic disease

Scientific American November 13, 2002  William R. Leonard