Genes, Metabolism, and Behavior: Interacting Networks

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Drosophila (the fruit fly):
A model system
~ 20-30,000 genes in human genome
(not very many)
~14,000 genes in Drosophila genome
similar to humans in > 50% of gene sequences and in cellular mechanisms
If there are relatively few genes, network combinations are important.
For example:

Temperature-sensitive *syntaxin* (*syx*) mutant

For example:
Identification of interacting genes (suppressors)

van Swinderen and Greenspan (2005)
Interactions among suppressor genes

Sup1 + Sup2

van Swinderen and Greenspan (2005)

Time at 38°C

% standing

Observed

Expected
Interactions among suppressor genes (without original $syx^-$ mutation)

**Sup1**

**Sup2**

**Sup3**

**Sup4**

**Sup5**

**Sup6**

**Sup7**

**Sup8**

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negative interaction

positive interaction
Interactions among suppressor genes
(with original syx⁻ mutation)
Interactions among suppressor genes
(with original $syx^-$ mutation)

new interaction
In networks, small changes ramify widely.
How do gene networks interact with metabolic networks?

DIET

NUTRIENTS

METABOLISM

SIGNAL TRANSDUCTION

GENE EXPRESSION

NORMAL CELL GROWTH
How does genotype interact with these networks?
Genes and Food-Related Behavior

\[ \text{foraging gene (2 natural variant forms)} \]

Drosophila larvae
Genes and Food-Related Behavior

w foraging gene (2 natural variant forms)

*Rovers* explore more in the presence of food
(no difference in absence of food)
Genes and Food-Related Behavior

- *Rovers* and *sitters* differ only in one gene
Genes and Food-Related Behavior

- Rovers and sitters differ only in one gene

- The difference is subtle:

  *Rovers* have slightly more (12%) of the enzyme cGMP-dependent protein kinase than *sitters*
Many enzymes in citric acid cycle higher in sitters.
The metabolite acetyl-carnitine is affected by the citric acid cycle.
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Acetyl-carnitine is a non-essential nutrient taken as a dietary supplement for:
- athletic performance enhancement
- chronic fatigue syndrome
- male infertility
- Alzheimer’s disease
The metabolite acetyl-carnitine is affected by the citric acid cycle.

Acetyl-carnitine is a non-essential nutrient taken as a dietary supplement for:

- athletic performance enhancement
- chronic fatigue syndrome
- male infertility
- Alzheimer’s disease

Rovers do not respond to acetyl-carnitine, sitters do.
Genes and Metabolism

- A small genetic difference can produce a large metabolic and behavioral difference.
Genes and Metabolism

- A small genetic difference can produce a large metabolic and behavioral difference.

- The foraging variants differ in their response to nutrients.
Genes and Metabolism

- A small genetic difference can produce a large metabolic and behavioral difference.
- The foraging variants differ in their response to nutrients.
- Network changes ramify widely.
A Shifting Genetic/Metabolic Landscape
Any trait involves many genes.
Change percolates through the system…
...differing with each change.
Understanding the network
Translating findings from *Drosophila* to humans
**Human Obesity/Diabetes genes differing in Rover vs. sitter**

<table>
<thead>
<tr>
<th>Human Gene(s)</th>
<th>Drosophila cognate gene(s)</th>
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</thead>
<tbody>
<tr>
<td>Leptin LEP, OB</td>
<td>CG9611</td>
</tr>
<tr>
<td>AgRP</td>
<td>LanA - elav, spz</td>
</tr>
<tr>
<td>Neuropeptide Y NPY3R</td>
<td>Npf</td>
</tr>
<tr>
<td>Adiponectin APM1, GBP28</td>
<td>Cg25C</td>
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<tr>
<td>Resistin FIZZ3, RETN</td>
<td>drpr - Draper - InR group</td>
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<tr>
<td></td>
<td>CG3984 - InR group</td>
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<tr>
<td></td>
<td>crb - Toll group</td>
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<tr>
<td></td>
<td>CadN - wupA, syx1A</td>
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<tr>
<td>Tnf-alpha TNFRSF10B, DR5</td>
<td>imd - Toll, Pten, Cam</td>
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<tr>
<td>IL7R</td>
<td>cycA, hiw</td>
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<tr>
<td>IL1RAPL</td>
<td>Toll</td>
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<tr>
<td>IRAK4</td>
<td>pelle</td>
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Clement, Sokolowski, Greenspan and Phenomenome Discoveries
Personalized Nutrition: the Future of Nutrigenomics

- Nutrients can modify DNA structure, gene expression, and metabolism
Personalized Nutrition: the Future of Nutrigenomics

- Nutrients can modify DNA structure, gene expression, and metabolism
- Individual genetic variation can determine the response to the nutritional environment
Personalized Nutrition: the Future of Nutrigenomics

- Nutrients can modify DNA structure, gene expression, and metabolism
- Individual genetic variation can determine the response to the nutritional environment
- Genomic technology can be applied to assess and predict nutrient-gene interactions that can lead to development of disease
Opportunities and Challenges in Nutrition Research

Chronic disease results from polygenic, multi-factorial interactions
Opportunities and Challenges in Nutrition Research

- Chronic disease results from polygenic, multifactorial interactions
- The impact of nutrient-gene interactions on disease progression is not well understood
Opportunities and Challenges in Nutrition Research

- Chronic disease results from polygenic, multifactorial interactions
- The impact of nutrient-gene interactions on disease progression is not well understood
- Nutrigenomics offers a dynamic approach for revealing the relationship between genes, nutrients, and risk for chronic disease