Obesity: Current Topics in Genetics

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Learning Objectives

1. Be familiar with the evidence for genetic influences on obesity

2. Understand how genetic factors can influence obesity, both directly and indirectly

3. Be familiar with one current application of genomic information for public health practice
Outline

1. Background
2. Genetics of Obesity
   • Animals
   • Humans
3. Indirect genetic influences
   • Genetics of Taste
   • Nutrigenomics
   • Pharmacogenomics
4. Family History
5. Summary
6. Evaluation
Public Health Importance

• Mortality
  – Increased risk of premature death

• Morbidity
  – Diabetes, Heart disease, Hypertension, some Cancers, Breathing Problems, Ischemic Stroke, Arthritis, and Reproductive Complications

• Prevalence
  – 59 million (30%) Americans are obese (BMI>= 30)
  – Rates are increasing faster than ever (epidemic proportions)
Trends in Obesity

From the CDC website: BRFSS Trends Data
Trends in Obesity

Figure 2. Age-adjusted* prevalence of overweight and obesity among U.S. adults, age 20-74 years

- Overweight or obese (BMI ≥ 25.0)
- Obese (BMI ≥ 30.0)

<table>
<thead>
<tr>
<th></th>
<th>NHANES II (1976-80) n=11,207</th>
<th>NHANES III (1988-94) n=14,468</th>
<th>NHANES (1999-00) n=3,601</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight</td>
<td>47</td>
<td>56</td>
<td>64</td>
</tr>
<tr>
<td>Obese</td>
<td>15</td>
<td>23</td>
<td>31</td>
</tr>
</tbody>
</table>

*Age-adjusted by the direct method to the year 2000 U.S. Bureau of the Census estimates using the age groups 20-39, 40-59, and 60-74 years.

From the CDC Website: NHANES Study Data
Risk Factors for Obesity

- Diet: high calorie and low nutrient dense foods
- Physical Inactivity
- Age
- Socioeconomic status
- Certain medical conditions and medications
- Race
- Smoking cessation
- Family History
- Genetic susceptibility
Rodent Models of Obesity
Parabiosis Experiment: \textit{ob} and \textit{db} mice

Summary of parabiosis experiments with the \textit{ob/ob} and \textit{db/db} mice.
\textit{ob/ob}: leptin deficiency \hspace{1cm} \textit{db/db}: mutation in leptin receptor

By Pamela Hunt, Amgen Inc.
Available at: http://www.biotech-medecine.com/archives/review14/point
### Rodent Strains with Monogenic Forms of Obesity

<table>
<thead>
<tr>
<th>Strain</th>
<th>Inheritance</th>
<th>Encoded Protein</th>
<th>Defect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obese ((ob))</td>
<td>Mouse</td>
<td>Recessive</td>
<td>Leptin</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stop codon/promoter defect in leptin</td>
</tr>
<tr>
<td>Diabetes ((db))</td>
<td>Mouse</td>
<td>Recessive</td>
<td>Leptin receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Defect lepR</td>
</tr>
<tr>
<td>Agouti yellow ((a^y))</td>
<td>Mouse</td>
<td>Dominant</td>
<td>Agouti</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ectopic expression of melanocortin receptor antagonist</td>
</tr>
<tr>
<td>Tubby ((tub))</td>
<td>Mouse</td>
<td>Recessive</td>
<td>Phosphodiesterase</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Apoptosis in the brain?</td>
</tr>
<tr>
<td>Fat</td>
<td>Mouse</td>
<td>Recessive</td>
<td>Carboxypeptidase E</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Carboxypeptidase E activity abolished</td>
</tr>
<tr>
<td>Zucker/fatty ((fa))</td>
<td>Rat</td>
<td>Recessive</td>
<td>Leptin receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Defect lepR</td>
</tr>
<tr>
<td>Koletsky ((kol))</td>
<td>Rat</td>
<td>Recessive</td>
<td>Leptin receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Defect lepR</td>
</tr>
<tr>
<td>Corpulent ((cp))</td>
<td>Rat</td>
<td>Recessive</td>
<td>Leptin receptor</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Defect lepR</td>
</tr>
</tbody>
</table>

From: Diabetes Mellitus A Fundamental and Clinical Text (3rd Ed.) D. LeRoith, S.I. Taylor and J.M. Olefsky, Lippincott Williams & Wilkins, 2004, Philadelphia
Evidence for genetic influences: Humans

- Familial aggregation
  - familial clustering of obesity in families

- Twin Studies
  - greater concordance among MZ twins compared to DZ twins

- Family Studies
  - variety of “statistical models” consistent with genetic influences
The Search for Obesity Susceptibility Genes

“I found one! I found one!”

Kenneth M. Weiss & Joseph D. Terwilliger

nature genetics • volume 26 • October 2000
Candidate Genes and Single Gene Disorders: Chromosomal Location

Image adapted from:
### Major Phenotypic Features of Monogenic Forms of Human Obesity

<table>
<thead>
<tr>
<th>Gene</th>
<th>Obesity</th>
<th>Birth weight</th>
<th>Endocrine abnormalities</th>
<th>Hyperphagia</th>
<th>Inheritance</th>
<th>Chromosome</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>LEP</em></td>
<td>Severe</td>
<td>Normal</td>
<td>Low leptin, Hypogonadism, High thyroid-stimulating hormone, High insulin</td>
<td>+</td>
<td>Recessive</td>
<td>7q31.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High leptin, Pituitary dysfunction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>LEPR</em></td>
<td>Severe</td>
<td>?</td>
<td>Hypogonadotrophic hypogonadism, Sympathetic dysfunction, High Insulin</td>
<td>+</td>
<td>Recessive</td>
<td>1p31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Red hair pigmentation, ACTH deficiency, hypocortisolism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>POMC</em></td>
<td>Severe</td>
<td>Normal</td>
<td>ACTH deficiency, hypocortisolism</td>
<td>+</td>
<td>Recessive</td>
<td>2p23.3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Low $\alpha$-MSH, Hypogonadotrophic hypogonadism, Hypocortisolism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Postprandial hypoglycemia, High POMC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>PC1</em></td>
<td>Severe</td>
<td>?</td>
<td>High proinsulin, low insulin, Postprandial hypoglycemia</td>
<td>?</td>
<td>Recessive</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>High POMC</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>MC4-R</em></td>
<td>Severe</td>
<td>Normal</td>
<td>Not observed</td>
<td>+</td>
<td>Dominant</td>
<td>18q22</td>
</tr>
<tr>
<td><em>NROB2</em></td>
<td>Mild</td>
<td>High</td>
<td>Mild hyperinsulinemia</td>
<td>-</td>
<td>Dominant</td>
<td>1p36.1</td>
</tr>
</tbody>
</table>

**LEP**, leptin; **LEPR**, leptin receptor; **POMC**, pro-opiomenocortin; **PC1**, prohormone convertase1; **MC4-R**, melanocortin-4 receptor; **ACTH**, adrenocorticotropic hormone; $\alpha$-**MSH**, $\alpha$-melanocyte-stimulating hormone.

From: Diabetes Mellitus A Fundamental and Clinical Text (3rd Ed.) D. LeRoith, S.I. Taylor and J.M. Olefsky, Lippincott Williams & Wilkins, 2004, Philadelphia
Leptin Therapy: From mice to humans

Left: Ob mouse 6 weeks post leptin therapy
Right: Ob mouse 6 weeks post saline injections

A child with a mutation in the leptin gene before and after leptin therapy


Genetics of Human Obesity

• Common form(s) of obesity are likely due to complex interactions between genes and environment
  - body fat pattern
  - appetite regulation
  - other pathways

• Rare monogenic forms do not account for majority of cases

• Genes can also indirectly influence obesity through a variety of mechanisms
Genetic taste markers

- Taste responsiveness to PTC and PROP is heritable
- Nontasters, regular tasters and supertasters
  - 70% of US population are tasters
  - Higher percentage of tasters among Africans and Asians
- Ability to taste PTC or PROP is associated with a reduced acceptance of some foods
  - Fruits and vegetables containing phytonutrients
- Genetic taste markers may serve as markers for health and disease
- Genetic taste makers may have relevance for public health activities
Supertasters: Food Dislikes

- raw cruciferous vegetables and some green vegetables (broccoli, cabbage, Brussels sprouts, spinach, kale)
- sharp cheeses
- dark chocolate
- Japanese green tea
- grapefruit and lemon juice
- dry wine
- beer
- black coffee / tea
- tonic water
Are you a Supertaster?

- Remove a single taste strip included in your packet of materials
- Have a beverage available
- Place the filter paper on the middle of your tongue
- Rate your response as:
  1 (no taste)  2 (bitter)  3 (very bitter)
Link between genetic taste markers and BMI?

• Inconsistent evidence for an association between taster status and BMI
  - no association between taster status and BMI
  - nontasters and regular tasters were heavier than supertasters after accounting for dietary restraint

• Many factors influence food preference and dietary intake

Public Health Implications:
Dietary intervention strategies aimed at improving diet quality should include taste preferences, as well as a wide range of demographic, economic and sociocultural variables
Nutrigenomics

Integrates genomics and nutrition

• **Goal:** Improving health and preventing disease through tailored diet and lifestyle prescriptions

• **Concerns:**
  - Private companies offering “genetic personalization products”
    - Personalized advice on nutritional requirements and optimal exercise/training programs
    - No evidence for efficacy
    - Misleading claims
    - Biobanking DNA
Pharmacogenomics

• Tailoring of drug treatment according to individual genotype

• Certain medications are known to be more (or less) effective in patients with a particular genetic profile

• **Example**: Leptin therapy for obese patients with a mutation in their leptin gene

• **Concerns**:
  - Access
  - Increase in health disparities
Prevention Efforts

1. Dietary modification coupled with regular physical activity
   - Modest enough to be acceptable, but robust enough to produce meaningful changes
   - Maintain healthier habits

2. Approach
   - All Inclusive population approach?
     - general educational campaign
   - Target specific sub-groups?
     - incentive to follow regime should be higher than for general population

3. Genomic Tools
   - Family history as a bridge from genetics to genomics
Rationale for using Family History as a Public Health Tool

1. Screening for single major gene(s) is unlikely
2. Reflects unique Genomic information
   - genomic, ecologic, behavioral and interactions
3. Effective interventions
4. Identify individuals for targeted intervention
5. Family-Centered approaches
Positive Family History and Risk of Obesity

Study

(1st author, at risk group, affected relative)

Relative Risk
CDC Family History Public Health Initiative

• CDC OGDP, in collaboration with several CDC programs and NIH Institutes

• Evaluate the use of family history information
  • assessing risk for common diseases
  • influencing early detection and prevention strategies

• Evaluation Framework proposed in early 2002
  • Yoon PW et al., Genet in Med 2002;4:304-310

• 3 Components: Workgroups, Tool development, Research agenda

• Panel of experts convened to review what is known about family history as a risk factor for selected diseases
  • Feb 2003 issue of American J of Preventative Medicine
Family Medical History

• Several family medical history initiatives
  - CDC Family History Initiative
  - National Coalition for Health Professional Education in Genetics (NCHPG)
  - Surgeon General’s new public health campaign

• “Surgeon General’s American Family Health Initiative”
  - to be announced before Thanksgiving
  - web and paper based tool to collect family medical history information
Implications

Potential Benefits of genetic information:
• Identify subgroups who might be particularly responsive or resistant to environmental or pharmacologic intervention
• Better understanding of the mechanisms involved in obesity
• Motivate positive behavior change

Potential Harms of genetic information:
• Focus away from environmental factors can have negative consequences
• Focus on “genetic” factors can lead to fatalism
• Potential for increase in health disparities
Summary

- Genes
- Environment
- Genomic tools
- New technologies
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http://depts.washington.edu/cgph

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