Genetics of Obesity

Washoe County Obesity Forum
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• No disclosures

Impact of Obesity: Society

• Obesity is the most significant contributor to ill health worldwide (WHO)

• More than 30% of US adults are obese (CDC)

• 1987: 18% of health care expenditures in US attributable to obesity-related diseases (CBO)

2007: 32%
Impact of Obesity: Individuals

- Cardiovascular disease
- Pulmonary diseases (ex. Sleep apnea)
- Metabolic diseases (ex. Diabetes)
- Arthritis
- Cancer
- Psychiatric illness
Causes of Obesity

Environmental
- Low-cost, calorie-dense food
- Sedentary lifestyle
- Limited nutrition and fitness education

Genetic
- Single gene disorders
- Polygenic interactions
- Epigenetics
Evidence for a Genetic Influence

• Evolution:
  • Many genes involved in glucose and lipid metabolism have been subject to positive selection over the last 10,000 years

• Heritability:

![Heritability Bar Chart]

- Autism
- Schizophrenia
- Obesity
- Depression
- Hypertension
Monogenic Influences

- **Autosomal recessive**
  - Carrier father
  - Carrier mother
  - Affected child
  - Carrier child
  - Unaffected child

- **Autosomal dominant**
  - Affected father
  - Unaffected mother
  - Affected child
  - Unaffected child
  - Unaffected child

- **X-linked recessive, carrier mother**
  - Unaffected father
  - Carrier mother
  - Affected son
  - Unaffected daughter
  - Unaffected daughter
  - Carrier daughter
  - Affected son

Source: U.S. National Library of Medicine
Monogenic Influences

• Genes involved in regulation of appetite account for ~5% of human obesity

• At least 30 single gene disorders have obesity as a characteristic clinical finding
Polygenic Influences

• Obesity is usually a complex genetic trait

• 2005 Human Obesity Gene Map:
  • 253 genetic loci associated with obesity
  • 22 of these supported by at least 5 positive studies
  • Loci on every chromosome except Y
## Polygenic Influences

### Table 1. Genes with five or more positive associations of variants with obesity or obesity-related phenotypes in the published literature [adapted from (31)]

<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>Full name</th>
<th>Chromosomal location</th>
<th>Number of studies</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE</td>
<td>Angiotensin I-converting enzyme (peptidyl-dipeptidase A) 1</td>
<td>17q24.1</td>
<td>6</td>
<td>0.05 – 0.0023</td>
</tr>
<tr>
<td>ADIPOQ</td>
<td>Adiponectin, C1Q and collagen domain containing</td>
<td>3q27</td>
<td>11</td>
<td>0.05 – 0.001</td>
</tr>
<tr>
<td>ADRB2</td>
<td>Adrenergic, beta-2;, receptor, surface</td>
<td>5q31–q32</td>
<td>20</td>
<td>0.05 – 0.0001</td>
</tr>
<tr>
<td>ADRB3</td>
<td>Adrenergic, beta-3;, receptor</td>
<td>8p12–p11.2</td>
<td>29</td>
<td>0.05 – 0.001</td>
</tr>
<tr>
<td>DRD2</td>
<td>Dopamine receptor D2</td>
<td>11q23.2</td>
<td>5</td>
<td>0.03 – 0.002</td>
</tr>
<tr>
<td>GNB3</td>
<td>Guanine nucleotide binding protein (G protein), beta polypeptide 3</td>
<td>12p13.31</td>
<td>14</td>
<td>0.05 – 0.001</td>
</tr>
<tr>
<td>HTR2C</td>
<td>5-hydroxytryptamine (serotonin) receptor 2C</td>
<td>Xq24</td>
<td>10</td>
<td>0.05 – 0.0001</td>
</tr>
<tr>
<td>IL6</td>
<td>Interleukin 6 (interferon, beta 2)</td>
<td>7p21</td>
<td>6</td>
<td>0.03 – 0.003</td>
</tr>
<tr>
<td>INS</td>
<td>Insulin</td>
<td>11p15.5</td>
<td>7</td>
<td>0.05 – 0.0002</td>
</tr>
<tr>
<td>LDLR</td>
<td>Low density lipoprotein receptor (familial hypercholesterolaemia)</td>
<td>19p13.2</td>
<td>5</td>
<td>0.04 – 0.001</td>
</tr>
<tr>
<td>LEP</td>
<td>Leptin (obesity homologue, mouse)</td>
<td>7q31.3</td>
<td>10</td>
<td>0.05 – 0.003</td>
</tr>
<tr>
<td>LEPR</td>
<td>Leptin receptor</td>
<td>1p31</td>
<td>16</td>
<td>0.04 – 0.0001</td>
</tr>
<tr>
<td>LIPE</td>
<td>Lipase, hormone-sensitive</td>
<td>19q13.2</td>
<td>5</td>
<td>0.05 – 0.002</td>
</tr>
<tr>
<td>MC4R</td>
<td>Melanocortin 4 receptor</td>
<td>18q22</td>
<td>8</td>
<td>0.04 – 0.002</td>
</tr>
<tr>
<td>NR3C1</td>
<td>Nuclear receptor sub-family 3, group C, member 1 (glucocorticoid receptor)</td>
<td>5q31</td>
<td>10</td>
<td>0.05 – 0.001</td>
</tr>
<tr>
<td>PLIN</td>
<td>Perilipin</td>
<td>15q26</td>
<td>5</td>
<td>0.05 – 0.0008</td>
</tr>
<tr>
<td>PPARG</td>
<td>Peroxisome proliferative activated receptor, gamma</td>
<td>3p25</td>
<td>30</td>
<td>0.05 – 0.001</td>
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<tr>
<td>RETN</td>
<td>Resistin</td>
<td>19p13.2</td>
<td>5</td>
<td>0.048 – 0.001</td>
</tr>
<tr>
<td>TNF</td>
<td>Tumor necrosis factor (TNF superfamily, member 2)</td>
<td>6p21.3</td>
<td>9</td>
<td>0.05 – 0.004</td>
</tr>
<tr>
<td>UCP1</td>
<td>Uncoupling protein 1 (mitochondrial, proton carrier)</td>
<td>4q28–q31</td>
<td>10</td>
<td>0.05 – 0.001</td>
</tr>
<tr>
<td>UCP2</td>
<td>Uncoupling protein 2 (mitochondrial, proton carrier)</td>
<td>11q13.3</td>
<td>11</td>
<td>0.05 – 0.001</td>
</tr>
<tr>
<td>UCP3</td>
<td>Uncoupling protein 3 (mitochondrial, proton carrier)</td>
<td>11q13</td>
<td>12</td>
<td>0.049 – 0.0005</td>
</tr>
</tbody>
</table>

Epigenetic Influences

- Epigenetics: heritable influences on genes that occur without a change in the DNA sequence
- Methylation
- Histone modification

Epigenetic Influences

- Prader Willi syndrome: insatiable appetite and rapid weight gain leading to obesity

http://library.thinkquest.org/06aug/00440/mpraderintro.html
Clinical Application

Public Health Perspective
Patterns
Statistics
Cause and Effect
... Across the population

Clinical Perspective
Risk Assessment
Management Plan
Improved Outcomes
... For individuals
Not All Obesity is Created Equal...

- Site of fat deposition
  - Higher levels of fat in and around insulin-sensitive tissues associated with more severe insulin resistance and chronic inflammatory state

- Hormonal and metabolic biomarkers
  - Some confer both a predisposition to obesity and protection against heart disease or diabetes
  - Predictive value
Obesity Biomarkers

- Genetic variants could serve as similar biomarkers

Genetic Variants as Obesity Biomarkers

- Stable over time
- Present before pathology
- More research needed
- Cost-effectiveness
- Genetic discrimination
What we thought we knew...

- Obesity is an environmental/social disease
  - There are significant genetic contributions to obesity; often the genetic influences interact with the environmental influences

- Obesity causes other health problems like diabetes, heart disease and cancer
  - Being obese does not necessarily mean being ill, and there are sub-types of obesity characterized by very specific pathologies
Thank You

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