GENES and TOBACCO USE

CAN GENES PREDICT WHO WILL...
- develop heart disease?
- develop lung cancer?
- become a smoker?
- be able to quit?

FACTORS CONTRIBUTING to TOBACCO USE

Environment
- Tobacco advertising
- Conditioned stimuli
- Social interactions

Physiology
- Genetic predisposition
- Coexisting medical conditions

Pharmacology
- Alleviation of withdrawal symptoms
- Weight control
- Pleasure

AVAILABLE EVIDENCE

- Adoption studies
- Twin studies
- Twins reared apart studies
- Linkage (family) studies

ADOPTION STUDIES

Adoption studies compare the similarities between
- Children who have been adopted and their biological parents versus children who have been adopted and their adoptive parents
  - OR -
- Adoptive sibling pairs versus biological sibling pairs

A D O P T I O N  S T U D I E S  (cont’d)

<table>
<thead>
<tr>
<th>Relationship</th>
<th>Correlation Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent and offspring</td>
<td>+ 0.21</td>
</tr>
<tr>
<td>Identical (monozygotic) twins</td>
<td>+ 0.52</td>
</tr>
<tr>
<td>Fraternal (dizygotic) twins</td>
<td>+ 0.30</td>
</tr>
<tr>
<td>Siblings</td>
<td>+ 0.11</td>
</tr>
<tr>
<td>Adoptive parents and adoptive offspring</td>
<td>- 0.02</td>
</tr>
<tr>
<td>Adoptive siblings</td>
<td>+ 0.05</td>
</tr>
</tbody>
</table>

Eysenck HJ, 1980.
TWIN STUDIES

Twin studies compare the similarities between

- Identical (monozygotic) twins and fraternal (dizygotic) twins

**Concordant or discordant?**
Higher concordance of tobacco use for identical than for fraternal twins

Estimated heritability for smoking = 0.53

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TWINS REARED APART STUDIES

- Combine aspects of adoption and twin studies
- Separate the effects of genetics from the effects of environment
- Have found that 60% of the variance in regular smoking in men and women born after 1940 is attributable to genetic factors (Kendler et al., 2000)

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LINKAGE STUDIES

- Use human genome mapping to enable researchers to identify genes associated with traits or disorders
- Examine family pedigrees to determine modes of inheritance of disorders
- Are more difficult when multiple genes have a role

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LINKAGE STUDIES (cont’d)

Linkage studies of smoking
1. Identify families with affected individuals (i.e., tobacco users)
2. Genotype two or more affected siblings and biological parents
3. Conduct linkage analysis to determine whether affected siblings are likely to share the same gene as the parents

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“CANDIDATE” GENES

- Candidate genes are genes hypothesized to contribute to the susceptibility for a trait or disorder.

- Two current lines of research in the area of candidate genes for smoking:
  - Genes affecting nicotine pharmacodynamics
  - Genes affecting nicotine pharmacokinetics

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**Pharmacology**

**Pharmacodynamics**

- Dopamine
  - Synthesis
    - Tyrosine hydroxylase
    - DRD1, DRD2, DRD3, DRD4, DRD5
    - Reuptake: Dopamine transporter (SLC6A3)
  - Metabolism
    - Catechol-O-methyltransferase
    - MAO A, MAO B
    - Dopamine β-hydroxylase

- Serotonin
  - Synthesis
    - Tryptophan hydroxylase (TPH)
  - Reuptake
    - Serotonin transporter (5-HTT)

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**Pharmacokinetics**

- Nicotine Metabolism
  - CYP2A6 enzyme
  - CYP2D6 enzyme

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**Genetic Effects on the Dopamine Reward Pathway**

**Genetic Effects on Nicotine Metabolism**

Reprinted with permission, Benowitz et al. (1994).

**Genes and Tobacco Use: Societal and Policy Implications**

- If genetic tests become available, should society encourage genetic testing for tobacco dependence?
  - Single gene or multiple gene?
  - Prevalence of the gene(s) in the population?
  - Is there an effective intervention to prevent smoking in those who are susceptible?
  - Impact of positive tests, and negative tests?

**Genes and Tobacco Use: Summary**

- Research in the area of genetics and smoking is in its infancy; however, there appears to be a genetic component to tobacco use.
- Tobacco use is a complex behavior, with many determinants.
- More research is needed.
- Genetic research and testing must proceed with caution because the societal stakes are high.

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