Genetic and Other Risk Factors for Alcoholism and Alcohol Abuse

Manzardo, Ch 11,12
Fingarette, pp 51-55
Suggestive Trends

- 80% of alcoholics in inpatient treatment have close relative with an alcohol problem.
- Five times greater risk among first-degree relatives of alcoholics than that of the general population.
  - Alcoholic Parents → 25% of sons and 5-10% of daughters become alcoholic.
  - General Population → 5% of sons and 1% of daughters.
Objectives of Genetic Investigations

- Detect and Quantify effects of Genetic Determinants on Problem Drinking
- Characterize Patterns of Inheritance
- Identify Genes that Confer Vulnerability
- Identify Factors other than Genes that affect pathogenisis of alcoholism
- Examine interaction between genetic factors and environment
Experimental Designs to Study Genetic/Environmental Factors among Twin and Non-Twin Siblings

<table>
<thead>
<tr>
<th></th>
<th>Average Genetic Sharing</th>
<th>Genetic Effects (G)</th>
<th>Shared Environment Effects (SE)</th>
<th>Nonshared Environment Effects (NSE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Identical twins reared together</td>
<td>100%</td>
<td>1.0</td>
<td>1.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Fraternal twins and full sibling pairs reared together</td>
<td>50%</td>
<td>0.5</td>
<td>1.0</td>
<td>0.0</td>
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<tr>
<td>Genetically unrelated siblings reared together</td>
<td>0%</td>
<td>0.0</td>
<td>1.0</td>
<td>0.0</td>
</tr>
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<tr>
<td>Total population variance</td>
<td>—</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Twin Studies: Concordance rates for DSM-III alcohol abuse/alcohol dependence among identical and fraternal twins.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Male Subjects</th>
<th>Female Subjects</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Identical</td>
<td>Fraternal</td>
</tr>
<tr>
<td>Alcohol abuse and/or alcohol dependence</td>
<td>0.76</td>
<td>0.61</td>
</tr>
<tr>
<td>Alcohol dependence</td>
<td>0.59</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Swedish Adoption Studies

- Incidence of Alcohol Problem among genetically unrelated individuals in same home environment
  - 2.5 fold increased risk for children of Alcoholic Parent
  - Type I -- most common, mild, adult onset, dependent on environment
  - Type II -- less common, severe, in men, early onset, aggressive behavior
  - Type III -- like Type II but lacks aggressive behavior
Animal Models
Alcohol Seeking Behavior

- Alcohol Preferring (P) and Alcohol non-Preferring (NP) Rats
  - bred through repeated generations to maximally exhibit this behavior
  - P rats will do anything to get alcohol -- very strong positive reinforcement -- despite harm

- Fast/Slow Mice
  - Fast mice quickly respond to stimulatory effects of alcohol
  - Slow mice do not respond initially to the stimulatory effect
  - Slow mice develop tolerance to depressive effect after 31 days and then are Stimulated
Molecular Biol. Properties of P/NP

- P/NP have comparative differences in LTW-4 protein
- LTW-4 variant present in P
- LTW-4 Protein increases in both P and NP with increased alcohol consumption
Response to Sedation Effects of Alcohol

- Long-Sleep/Short-Sleep mice
  - differ by righting reflex
  - LS loose righting reflex with 1/2 the alcohol level of SS
  - LS loose righting reflex with 1/30 the alcohol when admin. to Purkinge cells

- Biochemical Differences
  - LS more sensitive to alcohol augmentation of GABA function
  - GABA receptor in LS mice has enhanced alcohol activation
Withdrawal/Dependence

- Withdrawal-Seizure Prone (WSP) and Withdrawal-Seizure Resistant (WSR) mice
  - 10x more severe symptoms
  - no difference in sensitivity to other affects of alcohol including tolerance

- Biochemical Differences
  - Must be Genetic Component to Dependence
  - Glutamate receptors increase with alcohol consumption
  - WSP have more hippocampal NMDA (glutamate) receptors
Tolerance

- LS/SS tolerance differences
- P/NP differ in tolerance

- Biochemical Differences
  - Probably some combination of known differences--see earlier slides
Identifying Markers of Inherited Vulnerability

- Electrophysiology Markers
- Biochemical Markers
  - platelet monoamine oxidase and adenylate cyclase activities
  - rate of platelet serotonin uptake
- Differences in Reactions to Alcohol
  - alcohol-induced increase in baseline heart rate
  - alcohol-induced decreases in plasma prolactin and cortisol
Temperament and Behavior Risk Factors

- hyperactivity
- hyperactivity and aggression
- low attention span
- high task persistence
- labile emotional expressivity
- low ability to calm oneself following stress
- facile social behavior
Potential Benefits of Genetic Research Programs

Important implications for:
- Prevention
- Early Detection
- Treatment