Genetic and environmental influences on alcohol drinking behavior

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Genetic and Environmental Influences on Alcohol Drinking Behavior

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Guze Symposium
Washington University in St. Louis
February 19, 2004
Quantity-Frequency of Drinking: relationship to alcohol abuse and alcoholism

Predisposing and Protective Factors

Animal Models for Study of Alcoholism
Disease Burden by Illness - DALY United States, Canada and Western Europe, 2000
15 - 44 year olds

Cumulative Distribution of Alcohol Consumption in the United States

Source: Greenfield and Rogers; *J. Stud. Alcohol* 60:; 79-89, 1999
Alcohol-related health, personal, and social problems arise from drinking:

- too much too fast
- too much too often
Drinking Patterns: Rates and Risks

Moderate Drinking

Most people abstain or drink moderately placing them at low risk for alcohol use disorders. In general, Moderate Drinking is defined as 2 drinks/day for men; 1 drink/day for women (USDA/HHS dietary guidelines)

(One drink: one 12-ounce bottle of beer or wine cooler, one 5-ounce glass of wine, or 1.5 ounces of 80-proof distilled spirits)
Alcohol Abuse

A pattern of high-risk drinking that results in adverse outcomes, including:

- **Personal problems:** impact on memory and cognition; loss of employment, family, friends, and other significant relationships; increased risk for health problems and organ damage

- **Problems to others:** homicides, sexual assault, and other forms of interpersonal crime and violence; property damage; risk for injury and death

- **Problems for society:** illegal underage drinking; increased health care costs; loss of economic productivity; balancing economic, health, and social benefits, and risks of alcohol consumption
## Drinking Patterns

<table>
<thead>
<tr>
<th>Exceeds the daily limit</th>
<th>Percent of U.S. adults aged 18+</th>
<th>Abuse without dependence</th>
<th>Dependence with or without abuse</th>
</tr>
</thead>
<tbody>
<tr>
<td>less than once a week</td>
<td>16%</td>
<td>1 in 8 (12%)</td>
<td>1 in 20 (5%)</td>
</tr>
<tr>
<td>once a week or more</td>
<td>3%</td>
<td>1 in 5 (19%)</td>
<td>1 in 8 (12%)</td>
</tr>
<tr>
<td>both weekly &amp; daily</td>
<td>9%</td>
<td>1 in 5 (19%)</td>
<td>1 in 4 (28%)</td>
</tr>
</tbody>
</table>

Source: NIAAA National Epidemiologic Survey on Alcohol and Related Conditions, 2003
Drinking Patterns: Rates and Risks

Binge Drinking

The National Advisory Council on Alcohol Abuse and Alcoholism has recommended the following definition of “Binge Drinking”:

A “binge” is a pattern of drinking alcohol that brings blood alcohol concentration (BAC) to 0.08 gm% or above. For the typical adult, this pattern corresponds to consuming 5 or more drinks (male) or 4 or more drinks (female) in about 2 hours. Binge drinking is clearly dangerous for the drinker and for society.
Alcohol Dependence
(Alcoholism)

A common complex disease characterized by a persistent and progressive pattern of abnormally intense alcohol-seeking behavior that, over time, results in:

- loss of control over drinking
- a preoccupation with drinking
- the development of tolerance and dependence
Alcohol and Dependence

Genetic Susceptibility
- personality/temperament
- alcohol pharmacokinetic and pharmacodynamic responses

Environmental Exposure
- Quantity/Frequency
Why Some People Drink/Do Not Drink

- Reinforcing Effects
  - Positive
  - Negative
- Aversive Effects
- Peer/Cultural Influences
Why Some Drink More Than Others

Individual differences in:

- metabolism
- “level of response” to alcohol
- neuroadaptation (tolerance and/or sensitization with chronic drinking)
Why Some Drink Despite Negative Consequences

- Physical dependence (withdrawal)
- Psychological dependence (addiction)
Predisposing and Protective Factors
Initiation and Continuation of Drinking

- Environmental (familial and non-familial)
- Personality/Temperament
- Pharmacological effects of ethanol
Between Individual Variations in Responses to Alcohol

- Pharmacokinetics: absorption, distribution, and metabolism of alcohol
  
  3-4 fold

- Pharmacodynamics: subjective and objective responses to alcohol
  
  2-3 fold
**Protection Against Alcohol Dependence by ADH2*2 and ALDH2*2**

(Han Chinese Males in Taiwan)

<table>
<thead>
<tr>
<th></th>
<th>ADH2*2</th>
<th>ALDH2*2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonalcoholic (n=50)</td>
<td>0.73</td>
<td>0.30</td>
</tr>
<tr>
<td>Alcoholic (n=50)</td>
<td>0.48(^\dagger)</td>
<td>0.06(^\dagger)</td>
</tr>
</tbody>
</table>

\(^\dagger p < 0.001\)
Interaction Between the Functional Polymorphisms of Alcohol and Aldehyde Dehydrogenase in Protecting Against Alcoholism

Chen CC, Lu RB, Chen YC, Wang MF, Chang YC, Li T-K, and Yin SJ

<table>
<thead>
<tr>
<th></th>
<th>1/Odds Ratio of Risk*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADH1*1/<em>2 - ALDH2</em>1/*1</td>
<td>4.5</td>
</tr>
<tr>
<td>ADH2*1/<em>1 - ALDH2</em>1/*2</td>
<td>3</td>
</tr>
<tr>
<td>ADH2*1/<em>2 - ALDH2</em>1/*2</td>
<td>17</td>
</tr>
<tr>
<td>ADH2*2/<em>2 - ALDH2</em>2/*2</td>
<td>100</td>
</tr>
</tbody>
</table>

*Reference Group is ADH2*1/*1 - ALDH2*1/*1
Blood Acetaldehyde Concentrations After 0.2 g/kg Dose of Ethanol in Men with Different ALDH2 Allelotypes

Significant differences are seen between the homozygous groups and between them and the heterozygous group at almost all time points (n = 6 per group)
Aldehyde Dehydrogenase Genotypes in Japanese Alcoholics Over Time

<table>
<thead>
<tr>
<th>ALDH2 Genotypes</th>
<th>1979</th>
<th>1986</th>
<th>1992</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALDH2*2/*2</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>ALDH2*1/*2</td>
<td>2.5</td>
<td>8.0</td>
<td>13.0</td>
</tr>
<tr>
<td>ALDH2*1/*1</td>
<td>97.5</td>
<td>92.0</td>
<td>87.0</td>
</tr>
</tbody>
</table>

ADH2 Allele Frequency in Jews and Drinking Behavior

- ADH2*2 frequency is 0.02 in Israeli population (36% have at least one copy)
- ADH2*2 allele is associated with lower quantity and frequency of drinking

Age of Onset of Brain Disorders
Age at Onset of DSM-IV Alcohol Dependence

Percentage in each age group who develop first-time alcohol dependence

NIAAA National Epidemiologic Survey on Alcohol and Related Conditions, 2003
Prevalence of Lifetime Alcohol Dependence by Age of First Alcohol Use and Family History of Alcoholism

Genes That Predispose to and Protect Against Alcoholism

Genes Specific to Alcoholism

- ALDH2
- ADH2

alcohol metabolism

Genes for Endophenotypes and/or Disorders Co-occurring with Alcoholism

- COMT Val158met
  schizophrenia, alcohol dependence, heroin addiction, cognitive dysfunction, lower frontal P300 amplitude, diminished response to pain and stress

- SERT Ile425Val (chr 17)
  OCD and cluster of neuropsychiatric disorders including alcohol and other substance abuse/dependence, social phobia, anorexia

- GABRA2
  alcohol dependence and beta frequency of the EEG
Involvement of Cholinergic Muscarinic Receptor Gene (CHRM2) on Chromosome 7 in COGA* Families

. Significant linkage and linkage disequilibrium for frontal theta event-related oscillations that underlie P3 on chromosome 7 at CHRM2 (Jones, Porjesz, Almasy et al., *Int’l J. of Psychophysiology*, in press)

. CHRM2 gene may contribute to development of major depressive disorder in COGA families (Beirut, Wang, Hingrichs et al. Abstract Presented at World Congress of Psychiatric Genetics, 2003)

. Significant linkage and linkage disequilibrium for CHRM2 with alcohol dependence (Washington University COGA Group)

*Collaborative Project on the Genetics of Alcoholism*
Animal Models
## Rodent Lines Selected for Ethanol-Related Traits (Mice)

<table>
<thead>
<tr>
<th>Line/Species</th>
<th>Selection Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Long/Short Sleep (LS/SS)</td>
<td>Duration of loss of righting reflex after EtOH</td>
</tr>
<tr>
<td>Cold/Hot</td>
<td>Acute EtOH hypothermia</td>
</tr>
<tr>
<td>Fast/Slow</td>
<td>EtOH stimulated activity</td>
</tr>
<tr>
<td>Severe/Mild Ethanol Withdrawal (SEW/MEW)</td>
<td>Severity of withdrawal on a multivariate index</td>
</tr>
<tr>
<td>Withdrawal Seizure Prone/Resistant (WSP/WSR)</td>
<td>Severity of handling-induced convulsions after chronic EtOH</td>
</tr>
<tr>
<td>High/Low Alcohol Preference (HAP/LAP)</td>
<td>Preference for 10% EtOH solution</td>
</tr>
</tbody>
</table>
**Rodent Lines Selected for Ethanol-Related Traits (Rats)**

<table>
<thead>
<tr>
<th>Line/Species</th>
<th>Selection Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALKO Tolerant/Nontolerant (AT/ANT)</td>
<td>EtOH impairment of tilting-plane performance</td>
</tr>
<tr>
<td>High/Low Alcohol Sensitive (HAS/LAS)</td>
<td>Duration of loss of righting reflex after EtOH</td>
</tr>
<tr>
<td>ALKO Alcohol/Nonalcohol Preference (AA/ANA)</td>
<td>Preference for EtOH solutions</td>
</tr>
<tr>
<td>Preferring/Nonpreferring (P/NP)</td>
<td>Preference for 10% EtOH solution</td>
</tr>
<tr>
<td>High/Low Alcohol Drinking (HAD/LAD)</td>
<td>Preference for 10% EtOH solution</td>
</tr>
<tr>
<td>High/Low Alcohol Drinking (HARF/LARF)</td>
<td>Preference for 12% EtOH solution - limited access conditions</td>
</tr>
</tbody>
</table>
Selectively Bred Alcohol-Preferring Rats as Animal Model to Study Alcoholism

- Voluntarily consume 6-8g ethanol/kg/day
- Attain BACs of 0.05 – 0.25 g%
- Work to obtain the ethanol
- Consume ethanol for its pharmacological effects (not taste, smell, or calories)
- Develop tolerance with chronic drinking
- Develop physical dependence with chronic drinking
**Propensities of Animals with High Alcohol-Seeking Behavior**

Sensitive to the reinforcing/activating effects of ethanol (low/moderate dose)

Resistant to the aversive/impairing effects of ethanol (high dose)

Rapid development of tolerance to the high dose impairing effects of ethanol

Retains tolerance developed to the aversive impairing effects of ethanol
Intracranial Self-Administration
Lever Responses and Reinforcements for the ICSA of 25-200 mg % Ethanol by P and NP Rats

* P<0.05
Alcohol Deprivation Effect (ADE)

- Temporary increase in alcohol consumption following a period of alcohol deprivation
- Observed in rats, mice, monkeys, and humans
- Animal model for studying relapse
Comparison of Alcohol Consumption in Alcohol Preferring Rats and Humans

- The AER for the rat (400 mg/kg/h) is about 4x that for humans (100 mg/kg/h)

- Rats drinking 6 g/kg/d would be equivalent to humans drinking
  - 1.5 g/kg/day or
  - 105 g/70 kg person/day or
  - 8-9 drinks/day

- Rats drinking 16g/kg/d would be equivalent to humans drinking
  - 4g/kg/day or
  - 280 g/70kg person/day or
  - 23-24 drinks/day
## Animal Models in Alcohol Research

### Rodents: (Rats)

<table>
<thead>
<tr>
<th>QTL</th>
<th>Candidate Gene</th>
<th>Transgenic/Knockout</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P/NP</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol Preference (4:57 cM)</td>
<td>$\alpha$-synuclein</td>
<td>KO: ↓ consumption</td>
</tr>
<tr>
<td>Alcohol Consumption (chr 4)</td>
<td>Neuropeptide Y</td>
<td>KO: ↑ consumption; less sensitivity to sedative/hypnotic effects</td>
</tr>
<tr>
<td>HAD/LAD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol consumption (chr 10)</td>
<td>CREB</td>
<td>KO: ↑ consumption</td>
</tr>
</tbody>
</table>
ALCOHOLISM
Heterogeneity of Phenotypes

- Multiple environmental factors influence drinking behavior

- Multiple genes affect host susceptibility
  - Personality/mental function (antisocial behavior; CD; depression)
  - Ethanol pharmacogenetics (metabolism; CNS action; neuroadaptation)

- Different persons have different sets of susceptibility genes and experience different kinds of environmental provocation
Acknowledgements

Brenda G. Hewitt