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National Institutes of Health

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Genetic and Environmental Influences on Alcohol Drinking Behavior

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National Institute on Alcohol Abuse and Alcoholism
National Institutes of Health
Department of Health and Human Services

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>Drinking Pattern</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>Exceeds the <em>daily</em> limit less than once a week</td>
<td>16%</td>
<td>1 in 8 (12%)</td>
<td>1 in 20 (5%)</td>
</tr>
<tr>
<td>Exceeds the <em>daily</em> limit once a week or more</td>
<td>3%</td>
<td>1 in 5 (19%)</td>
<td>1 in 8 (12%)</td>
</tr>
<tr>
<td>Exceeds <em>both</em> weekly &amp; daily limits</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

Initiation of Drinking  Social Drinking  Alcoholic 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†</td>
<td>0.06†</td>
</tr>
</tbody>
</table>

†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

1/Odds Ratio of Risk*

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

<table>
<thead>
<tr>
<th>Gene</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>COMT</td>
<td>schizophrenia, alcohol dependence, heroin addiction, cognitive dysfunction, lower frontal P300 amplitude, diminished response to pain and stress</td>
</tr>
<tr>
<td>Val158met</td>
<td></td>
</tr>
<tr>
<td>SERT</td>
<td>OCD and cluster of neuropsychiatric disorders including alcohol and other substance abuse/dependence, social phobia, anorexia</td>
</tr>
<tr>
<td>ile425Val (chr 17)</td>
<td></td>
</tr>
<tr>
<td>GABRA2</td>
<td>alcohol dependence and beta frequency of the EEG</td>
</tr>
</tbody>
</table>
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</td>
<td>Severity of handling-induced convulsions after chronic EtOH</td>
</tr>
<tr>
<td>Prone/Resistant (WSP/WSR)</td>
<td>Preference for 10% EtOH solution</td>
</tr>
<tr>
<td>High/Low Alcohol Preference (HAP/LAP)</td>
<td></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
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
Repeated Deprivations – Concurrent EtOH Concentrations
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/70 kg 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>P/NP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol Preference (4:57 cM)</td>
<td>α-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