Genetic and Other Risk Factors for Alcoholism

Manzardo, Ch 11

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

	Average Genetic Sharing	Genetic Effects (G)	Shared Environment Effects (SE)	Nonshared Environment Effects (NSE)
Identical twins reared together	100%	1.0	1.0	0.0
Fraternal twins and full sibling pairs reared together	50%	0.5	1.0	0.0
Genetically unrelated siblings reared together	0%	0.0	1.0	0.0
Identical twins reared apart	100%	1.0	0.0	0.0
Fraternal twins and full sibling pairs reared apart	50%	0.5	0.0	0.0
Total population variance	—	1.0	1.0	1.0

Twin Studies: Concordance rates for DSM-III alcohol abuse/alcohol dependence among identical and fraternal twins.

Diagnosis	Male Subjects		Female Subjects	
	Identical	Fraternal	Identical	Fraternal
Alcohol abuse and/or alcohol dependence	0.76	0.61	0.36	0.25
Alcohol depencence	0.59	0.36	0.25	0.05

Pickens et al (1991) "Heterogeneity in the inheritance of alcoholism. A study of male and female twins." *Archives of General Psychiatry, 48,* p19-28

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 comon, severe, in men, early onset, agressive behavior
  - Type III -- like Type II but lacks agressive 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 both P and NP with increased alcohol consumption

Sedation

- Long-Sleep/Short-Sleep mice
  - differ by righting reflex
  - LS loose righting reflex with 1/2 the alcohol level of SS
  - LS looses 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--frog oocyte gene transfer

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

- hyperactivity
- hyperactivity and aggression
- low attention span
- task persistence
- labile emotional expressivity
- slow ability to calm oneself following stress
- facile social behavior

Potential Benefits of Genetic Research Programs

- Important implications for:
  - Prevention
  - Early Detection
  - Treatment