

# 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 pathogenesis of alcoholism
- Examine interaction between genetic factors and environment

# Experimental Designs to Study Genetic/Environmental Factors among Twin and Non-Twin Siblings

	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 dependence	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 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 loses righting reflex with 1/30 the alcohol when admin. to Purkinje 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