

Slide 1

GENETIC INFLUENCES IN ALCOHOLISM

**Reviews How a Range of
Genetically Influenced
Characteristics Increase
and Decrease the Risk**

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This title slide announces the aim of the lecture. The goal is to teach about genetic influences in complex disorders through using alcoholism as an example.

Slide 2

**GENETIC INFLUENCES
OPERATE IN:**

**Choice to Drink
Level of Response
Reinforcement
Consequences
DEPENDENCE**

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Genetic Influences

To understand genetic influences it is important to clearly state the characteristics that are the focus of study. While genetic influences have been observed for a wide range of characteristics, including the choice of whether to drink, levels of reinforcement, and so on, the major emphasis of this lecture will be on genetic influences in alcohol dependence.

Slide 3

DEPENDENCE

Any 3 of 7 in Same 12 months:
**Tolerance, Withdrawal, Use More or Longer,
Need Control, Much Time Spent, Give Up
Activities, Continued Use After Phys or
Psychol Probs**

ABUSE (If Not Dependent):

Any 1+ Problem in Same 12 months:
**Role Obligations, Hazardous Use, Legal,
Continues Despite Social/Interpers. Probs**

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Dependence

To understand the data, it is important to briefly define alcohol abuse and dependence (alcoholism). Slide 3 offers the DSM-IV definition of alcohol dependence and alcohol abuse. Most of the studies focusing on genetics of alcoholism have used definitions of dependence, although some have looked at the broad scope of abuse and/or dependence. Virtually none have studied genetic influences in abuse alone.

Dependence is defined as evidence of repeated life problems in at least three of seven major life areas occurring during the same twelve-month period. The time frame of occurrence of problems is used to demonstrate that a constellation of symptoms, or a syndrome, has occurred, rather than, for example, the development of one problem at age 17, another at age 27, and yet a third at 43. Abuse focuses on social, interpersonal, legal, or occupational problems, and is only to be diagnosed in individuals who do not meet criteria for dependence.

Slide 4

DATA SUPPORTING GENETIC INFLUENCES

4x ↑ Risk in 1° Relatives

MZ / DZ Concordance = 2 / 1

Adopted Away Children 4x ↑ Risk

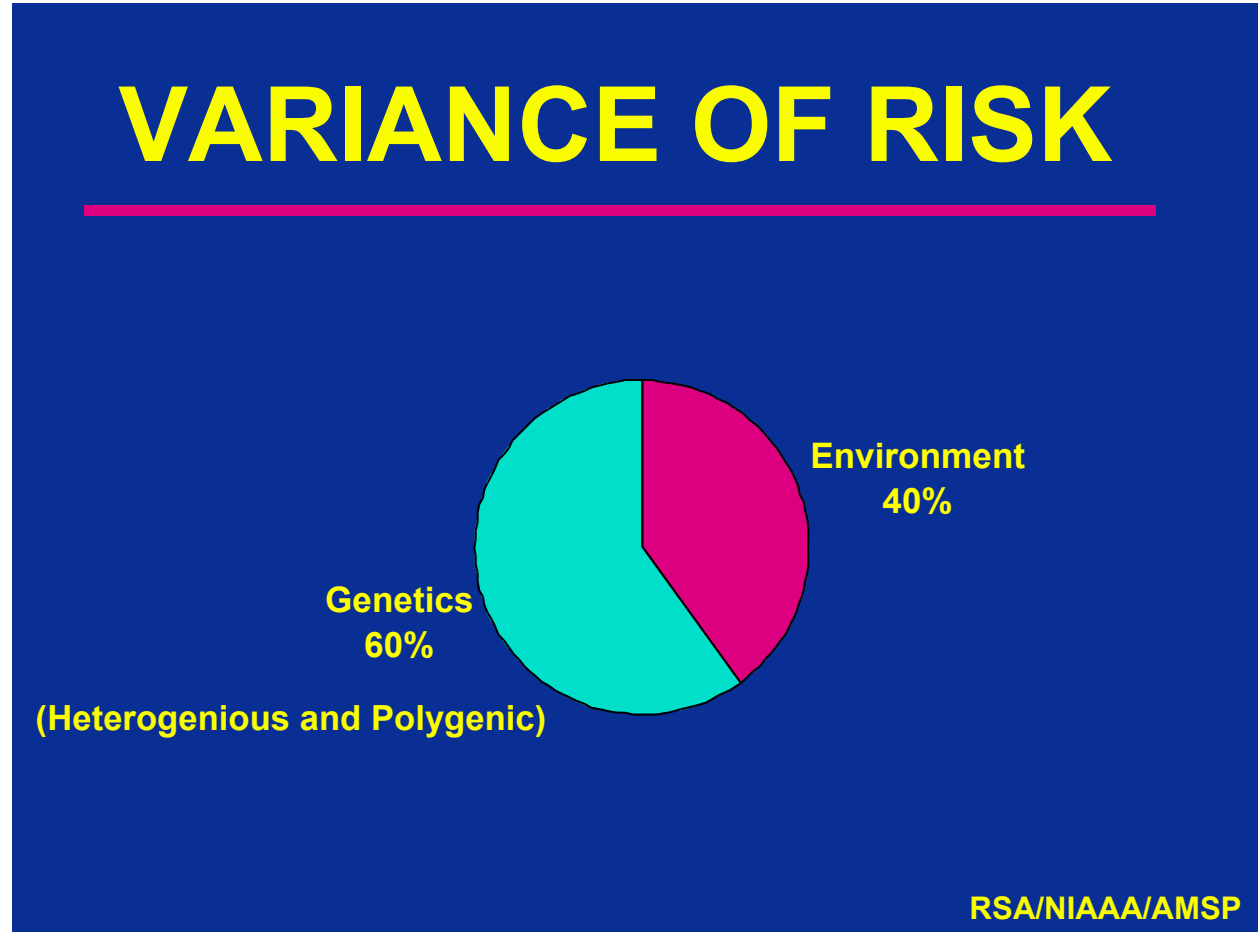
Animal Breeding / QTL Work

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Data Supporting Genetic Influences

The data supporting the importance of genetic influences in alcoholism include family, twin, adoption, and animal studies. These approaches are fairly typical of the types of studies used to determine genetic influences in any characteristic or disorder. First, almost all studies over the last 100 years have demonstrated an approximate four-fold increased risk for alcoholism in first degree (i.e., sharing 50% of genetic material) relatives of alcoholics. This same increased risk is observed in dizygotic (DZ) twins (who also share 50% of their genes), but is significantly higher in monozygotic (MZ) twins of alcoholic individuals (sharing 100% of genes). The increased risk for alcoholism still operates in offspring of alcoholics who are adopted away and raised without knowledge of their biological parents' problems. Finally, repeated heavy drinking, even to the point of problems in functioning, have also been demonstrated in animal models.

Slide 5



Variance of Risk

As a complex genetic disorder, environmental influences are likely to explain 40% of the alcoholism risk, while a combination of a variety of characteristics (genetically-influenced phenotypes) combine to explain the remaining 60%. Similar to genetic influences in most forms of cancer, adult-onset diabetes, high blood pressure, and so on, the risk for alcoholism relates to both genetic and environmental components. The biological influences are the focus of this lecture, but it is important to remember that environment (while more difficult to study) is also important. The major premise of this lecture is that multiple genetically-influenced characteristics contribute to the risk, many of these genetic influences operate independently of each other, and most of the phenotypes are influenced by multiple genes. When a few genes operate to influence the phenotype they are referred to as oligogenic, while when many genes contribute the phenomenon is called polygenic.

Slide 6

GENETIC FACTORS IN :

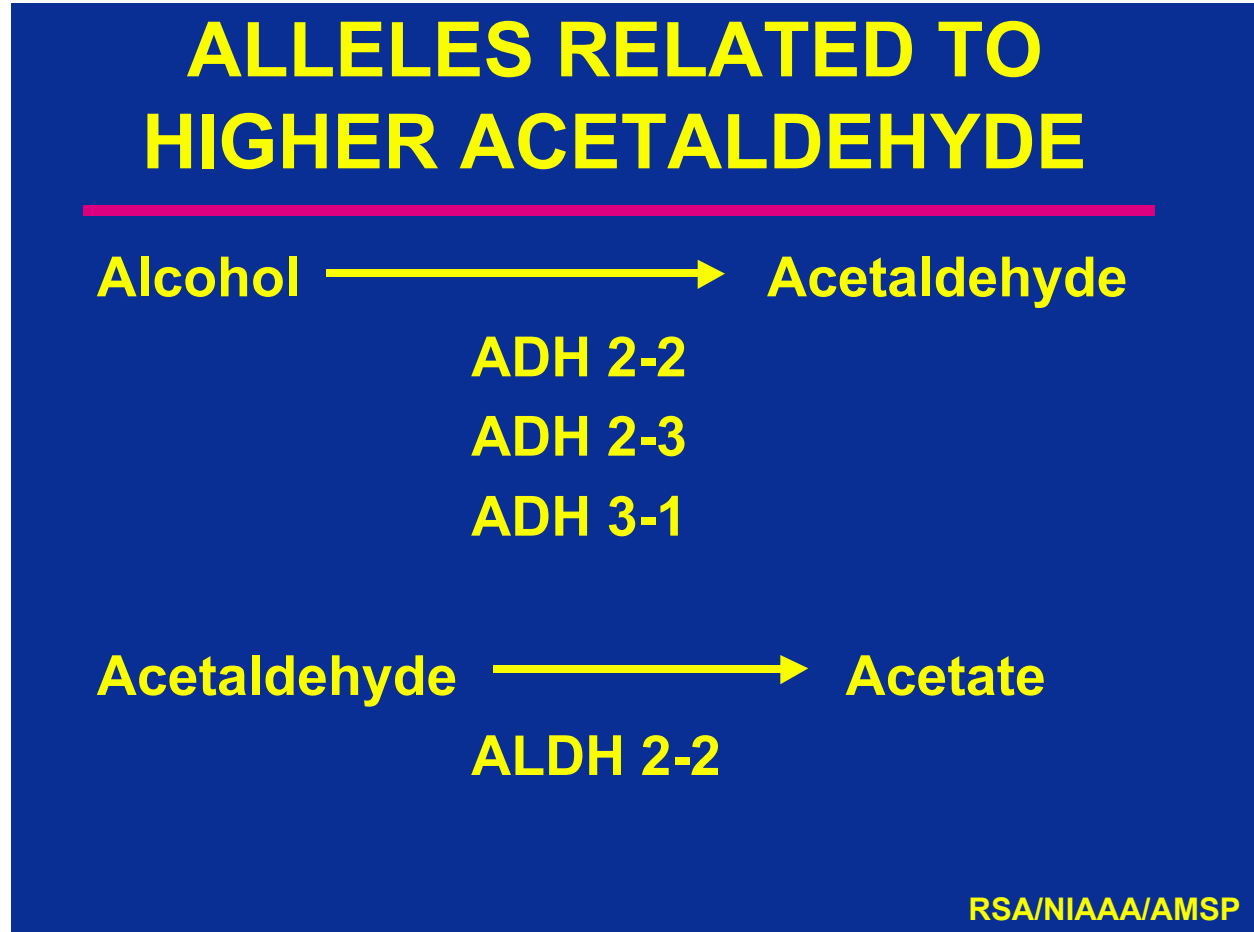
- I. Alcohol Metabolism
- II. Disinhibition / Impulsivity
- III. Level of Response to Alcohol
- IV. Independent Psychiatric Disorders
- V. Others
 - Opioids
 - CRF and the HPA
 - Neuropeptide Y
 - Etc.
 - Second Messenger Systems

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Genetic Factors

This lecture now turns to a series of characteristics or genetically-influenced phenotypes that appear to influence the alcoholism risk. As outlined on the slide, these include genes that influence alcohol metabolism; the phenomenon of disinhibition and/or impulsivity; the intensity or level of response to alcohol; independent major psychiatric disorders (which are defined later); and a variety of additional characteristics.

Slide 7



Alleles Related to Higher Acetaldehyde

The most thoroughly understood and best documented genetic influences in the alcoholism risk relate to alcohol metabolizing enzymes that increase the first breakdown product of alcohol (acetaldehyde), and thus help decrease the chances of repetitive heavy drinking and associated problems. The slide demonstrates that the metabolism of alcohol is relatively straightforward. This occurs through a variety of mechanisms, including the actions of catalase, the microsomal ethanol-oxidizing system (MEOS) and nonenzymatic pathways, but primarily through the actions of alcohol dehydrogenase (ADH) converting alcohol to acetaldehyde. This substance is potent and at low doses can be experienced as reinforcing. However, the major actions of acetaldehyde occur through modest to higher doses which produce vasodilatation, a more rapid heart rate, rapid increases or decreases in blood pressure, diarrhea, and other adverse effects. While ADH metabolizes approximately one drink (about 12 grams of ethanol) each hour, the acetaldehyde is usually rapidly destroyed through the actions of a very efficient mitochondrial form of ALDH, produced by the genetic allele ALDH2-1. Ten percent of Asian (Japanese, Chinese and Korean) men and women only produce an inactive form of ALDH2 (controlled by the allele ALDH2-2), and have very high levels of acetaldehyde even after very low doses of alcohol (perhaps one-half drink). These individuals have a zero risk for alcoholism. An

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additional 40% of Asian individuals are heterozygotes for the ALDH2 form (i.e., have both ALDH2-2 and ALDH2-1 alleles), demonstrating modest increases in acetaldehyde that are associated with a more intense (but not necessarily more aversive) reactions to alcohol. These men and women have a lower risk for alcoholism than nonflushing individuals, but their alcoholism rate can increase modestly but significantly if they move from a lower drinking to a higher drinking society.

Two alleles that produce forms of ADH that break down alcohol more rapidly (thus producing higher levels of acetaldehyde) can also be relevant to the alcoholism risk. These include ADH2-2, ADH2-3 and ADH3-1 alleles, with the first more commonly seen among Asians and the second among individuals of African heritage. The combination of the less efficient ALDH alleles and the more efficient ADH alleles can also be associated with higher levels of acetaldehyde after drinking and lower alcoholism risks in Asian men and women. There is some discussion of whether the more efficient ADH forms might also modestly decrease the alcoholism risk in Caucasian and African groups. When people with the enzyme forms related to higher acetaldehyde drink more heavily, they might increase their risk for organ damage and fetal alcohol effects.

These data are examples of specific genes that affect the alcoholism risk, in this instance having a protective effect. They also demonstrate the importance of both genetic material and environment. These genetic mechanisms influencing the alcoholism risk appear to act independently of the markers described elsewhere in this lecture, such as disinhibition and the intensity of response to alcohol.

Slide 8

POSSIBLE MARKERS FOR DISINHIBITION / IMPULSIVITY

P3 Amplitude

Conduct Disorder (CD)

Antisocial Personality (ASPD)

Type 2 + Type B

Dopamine: DRD2 / DRD4 / DAT

Low Serotonin (5-HT)

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Possible Markers for Disinhibition/Impulsivity

Cross-sectional and longitudinal studies have shown that aspects of impulsivity, evidence of possible neuronal disinhibition, and associated psychological attributes are seen in children of alcoholics and predict increased rates of alcoholism. Historically, these phenomena might have been first described regarding the relationship between conduct disorder (CD) in childhood (repetitive antisocial behaviors prior to the age of 15) followed by the antisocial personality disorder (ASPD) in adulthood (repetitive criminal activity, violence, problems maintaining long-term relationships, repeated difficulties in occupational functioning, etc.). Each of these is associated with very high rates of both alcohol and drug problems. Many of these characteristics, including higher levels of criminality and associated drug dependence also characterize hypothesized subtypes of alcoholism, including Type 2 and Type B. There is a substantial crossover between these conditions with associated high levels of impulsivity, sensation or novelty seeking, and difficulty learning from mistakes, and several neurophysiological phenomena, especially a low-amplitude P3 wave of the event-related potential (ERP). Some studies suggest that the low-amplitude P3 wave is likely to be a temporary phenomenon related to a delay in neuronal maturation, or a reflection of alcohol or life experience-induced depressive symptoms. In any event, most of these conditions (e.g.,

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ASPD.) and phenomena (eg., the amplitude of the P3 wave) are related to the alcoholism risk as is discussed in the next slide.

Several additional genetically-influenced characteristics have been hypothesized to be related to the alcoholism risk. These include lower levels of serotonin (5-HT) in the cerebrospinal fluid, a characteristic also seen in violent individuals, including those with ASPD. A complex literature has suggested that a specific genetic allele related to the dopamine2 receptor (DRD2) might also be associated with early onset, more severe alcoholism, and additional data suggest the possible importance of DRD4-related genes, and alleles that impact on forms of the dopamine transporter (DAT).

In presenting these materials it is important to remind the student it is possible that disinhibition/impulsivity might operate independently of genes that impact on lower levels of 5-HT or specific dopamine receptor alleles. However, it is also plausible that these characteristics all operate as part of a series of related genes that share an impact on the alcoholism risk through decreasing self-control in a heavy drinking environment, impairing the ability to learn from mistakes experienced earlier in the drinking career, or perhaps, through using alcohol to decrease levels of neuronal disinhibition and associated symptoms.

Slide 9

	ASPD	P3	DA Receptors	Low 5-HT
Genetic Influences	X	X	X	X
Overlap with Alcoholism	70%	30%	?	+
Predict Alcoholism	X	X	?	?

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Characteristics of Markers

The slide demonstrates a series of characteristics which are both genetically influenced and relate to the alcoholism risk. Low P3 amplitudes are seen in about 30% of children of alcoholics, and this marker helps predict later alcoholism. ASPD and CD are also genetically influenced and associated with higher rates of alcoholism. The background and references relevant to these items are presented in the context of the prior slide. The relationships among low serotonin levels, DRD2, and DRD4 receptors and violence of alcoholism is complex.

Slide 10

LEVEL OF RESPONSE (LR) TO ALCOHOL

**Observe Less Response When
Test with Alcohol (Human and
Animal)**

**Self Report of More Drinks for
an Effect**

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Level of Response (LR) to Alcohol

A second characteristic known to be both genetically influenced and to predict the risk for alcoholism is a low level of response to alcohol. This can be defined as a demonstration of lower amounts of change in cognitive, motor, electrophysiological, and hormonal measures after achieving standard blood alcohol levels, or as a self-report measure indicating the usual need for a higher number of standard drinks to achieve an effect. Several studies have addressed characteristics of the intensity of response to alcohol in animals and humans. In animal work, data have accumulated regarding the amounts of alcohol required to produce changes in body temperature, and/or intensity and length of action of effects such as sleep time. In humans, the majority of studies dealing with an estimated 1,000 or more subjects have used acute alcohol challenges that usually produce maximum blood levels of between 60 and 110 mg/dl (0.6 - 1.1 gm/dl), with most studies showing a low level of response to alcohol in those drinking but not yet alcohol-dependent offspring of alcoholics. On alcohol challenges the response to alcohol is measured as changes in feelings of intoxication, hormones, electrophysiological measures, and motor performance after drinking. A low response is also implied from a self-report of the need for more drinks to produce any of four effects of alcohol using the Self-Report of the Effects of Alcohol questionnaire (SRE).

Slide 11

LR

**Genetically Influenced
(Heritability \geq 40%)**

**Low LR in Animals, Twins, 1°
Relatives, 40% Offspring of
Alcoholics**

**Predicts Alcoholism over
4 - 20 Years**

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LR

The slide highlights genetic influences in the level of response to alcohol, the 40% of the offspring of alcoholics who demonstrate a low intensity of response to alcohol, as well as the series of studies that demonstrate the relationship between the intensity of response to alcohol and the later development of alcoholism.

Different strains of animals differ on their intensity of response to alcohol, and experiments have demonstrated the ability to selectively breed mice and rats that are exceptionally high or low in their level of response (LR) to alcohol. In humans, comparisons of MZ and DZ twins on LR, as well as evaluations of first, second degree, and unrelated individuals support the probability of a 40% to 60% heritability for LR.

Studies in the United States, Australia, and Denmark have shown that the LR earlier in life significantly predicts higher levels of alcohol-related life problems, including alcoholism, in the approximately 700 individuals who have been studied. Investigations generally report that lower intensities of response to alcohol are associated with higher risks of alcoholism, with some emphasizing the possibility that higher LR help protect from alcohol-related life problems.

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It is theorized that a low response to alcohol in individuals living in a heavy-drinking society might encourage higher intake of this drug in order to achieve the same levels of intoxication of others, a step that could contribute to the production of acquired tolerance and the existence of a heavy drinking peer group. It is also hypothesized that the need for higher doses of alcohol to have an effect might make it more difficult for an individual to learn to use internal cues to determine when it is appropriate to stop drinking on any given evening.

Slide 12

MARKERS POSSIBLY RELATED TO LR

EEG

Adenylyl Cyclase (AC)

Serotonin Transporter (5-HTT)

Protein Kinase C (PKC)

Neuropeptide Y (NPY)

Gamma Aminobutyric Acid (GABA)

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Markers Possibly Related to LR

A number of genetically-influenced characteristics have been reported to relate to both a potential enhanced alcoholism risk and a low intensity of response to alcohol. This is an opportunity to make two major points. First, the slide highlights a number of interesting phenomena that are genetically influenced and might relate to the alcoholism risk, perhaps in association with a low level of response to alcohol. Several of these markers are presented again later in the lecture. At the same time, the slide demonstrates how different and potentially unrelated biological mechanisms might contribute to similar phenotypes that enhance the alcoholism risk by producing similar clinical characteristics, such as a low response to alcohol.

The lecturer might choose to give additional detail about several of the phenomena described on the slide, although several of these are also highlighted in later slides as potentially independent phenomena. The list of references offered below offers background reading that might be of use in preparing this lecture. For example, more detail might be offered regarding recent findings on neuropeptide Y. Hypothesized to have an impact both on eating behaviors, as well as mood or anxiety symptoms, NPY is released in the presence of alcohol, in turn affecting the release of dopamine. Alcohol-preferring rats have a quantitative trait locus (QTL) on chromosome 4

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located in the area near where the gene affecting NPY has been mapped, and mice genetically engineered for an absence of NPY drink more alcohol and have a lower intensity of response to this drug.

Another characteristic that might be emphasized is the genes that control the production of protein kinase C epsilon (PKC). Alcohol-dependent individuals have been reported to have higher amounts of PKC, a form that might inhibit the actions of GABA_A receptors, with PKC knockout mice demonstrating both a high LR to alcohol at a lower self-administration of the drug.

Additional potential mechanisms related to both the alcoholism risk and a low LR include the serotonin transporter (SERT) and the 6 subunit of the GABA_A receptor (GABA₆). In addition, individuals who demonstrate low amounts of alpha activity or on the background cortical EEG overall low-voltage have also been shown to have an increased risk for alcoholism and a low level of response to alcohol.

Slide 13

INDEPENDENT PSYCHIATRIC DISORDERS

**40% of Alcoholics Carry Another
Diagnosis**

**Some are Temporary or Substance
Induced; ASPD; or Other Substance
Diagnoses**

**Higher than Expected Independent
Disorders Include:**

Bipolar

Schizophrenia

Panic Disorder

Social Phobia

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Independent Psychiatric Disorders

Another series of phenotypes that are both genetically influenced and related to a high alcoholism risk are independent (i.e., not just temporary and substance induced) major psychiatric disorders. Almost all studies indicate that alcoholic individuals have significantly elevated risks for other major psychiatric disorders. Even after excluding individuals who meet criteria for ASPD (which is associated with a high alcoholism risk described earlier) and those whose additional disorder is another substance dependence, about 40% of alcoholics do meet criteria for major mood, anxiety, psychotic, and other psychiatric syndromes. However, a substantial proportion of these are men and women demonstrate psychiatric symptoms only in the context of intoxication or withdrawal from alcohol. These temporary psychiatric conditions are referred to as substance-induced disorders in DSM-IV, and do not represent additional genetically-influenced conditions, but rather are part of the alcoholism itself.

Some independent psychiatric disorders (i.e., those seen in individuals who fulfill these syndromes either before the onset of alcoholism or during periods of extended abstinence) are related to the alcoholism risk. These include bipolar manic-depressive disease, schizophrenia, panic disorder, and social phobia. The lecturer might choose to discuss further how a careful

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time-line-based history can be used to differentiate between substance-induced and independent disorders. References are offered below to facilitate this information.

Slide 14

INDEPENDENT PSYCHIATRIC DISORDERS:

**Genetically Influenced
Might ↑ Alcoholism Risk By:**

Poor Judgement

Unemployment/Poverty

**Changes in Neurotransmitters
(eg.NPY,GABA,5-HT,DA)**

? “Self Medication”

? Linkage of Risk Factors

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Independent Psychiatric Disorders

The psychiatric disorders discussed in the prior slide are each genetically influenced and might increase the alcoholism risk through any or all of the variety of mechanisms presented on the slide. There is extensive literature that documents the importance of genetic influences in bipolar manic-depressive disease, schizophrenia, panic disorder, social phobia, and many other psychiatric conditions. These disorders appear to be independent of alcohol-metabolizing enzymes, the intensity of response to alcohol, and the psychiatric conditions listed in the slide are probably independent of disinhibition. It has been hypothesized that some people with these psychiatric disorders might increase their alcohol intake in an attempt to moderate their psychiatric symptoms, although there are few if any studies that directly support this intention. A second possible mechanism of relationship with alcoholism could occur through the disturbances in the neurochemical systems, such as serotonin, neuropeptide Y, and dopamine, which could then impact on the alcoholism risk. A third possibility is that genes that influence one or more of these disorders might be located near genes that influence the alcoholism risk and, thus, the predisposition towards both disorders might be inherited together, even though they might be mechanistically unrelated.

Slide 15

MARKERS RELATED TO SECOND MESSENGERS

Adenylyl Cyclase (AC)

G Proteins

Protein Kinase C (PKC)

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Markers Related to Second Messengers

The slide highlights the importance of second messenger systems as they relate to both the impact of alcohol on the cell and possible genetic influences on the alcoholism risk. The actions of adenylyl cyclase (AC), G proteins, and protein kinase C (PKC) help translate the impact of alcohol, neurotransmitters, and other substances on the cell membrane or receptors into actions within the cell. The G proteins facilitate the coupling of a variety of forms of AC to the receptors bound to the cell membrane, which then affects the production of cyclic adenosine-3'-monophosphate (c-AMP). Alcohol affects this system with some evidence that alcoholics and their relatives might have lower c-AMP production, perhaps related to a genetically-controlled reduced binding of the more stimulatory form of the G proteins. Similarly, there have been reports of diminished AC functioning in alcoholics and their relatives, including studies in children of alcoholics. One theory attempts to pull these findings together by hypothesizing that the risk for alcoholism might be related to a low innate activity of the stimulatory form of G proteins, with alcohol compensating by causing a temporary stimulation of the system, with subsequent abstinence intensifying the deficit and, thus, encouraging more alcohol intake. These findings might also have an impact on the role that alcohol plays in decreasing neuronal

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excitability to the enhancement of G protein-coupled inwardly-rectifying potassium channels (GIRKS).

PKC is also important in the effects of alcohol and the translation of the impact of various neurotransmitters. Alcoholics have been reported to have higher amounts of PKC that inhibits GABA_A receptors. PKC -deficit (knockout) mice have both a high sensitivity to alcohol and a lower self-administration of alcohol in free-choice situations.

These phenomena might impact on several other characteristics of the alcoholism risk already described in this lecture. Prominent among these is the possibility that the reported findings in these systems relate to a lower intensity of response to alcohol.

Slide 16

ADDITIONAL POSSIBLE MARKERS

OPIOID SYSTEM

NEUROPEPTIDE Y

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Additional Possible Markers

Two additional interesting markers possibly related to the alcoholism risk involve the opioid systems and the neurotransmitter, neuropeptide Y (NPY). Once again, these two markers might stand by themselves in relationship to the alcoholism risk, or might perform as part of additional families of findings (e.g., NPY and the low response to alcohol).

First, there are interesting potential relationships between the alcoholism risk and opioid systems. Acute alcohol produces the release of endogenous opioids, alcohol-preferring animals have a greater amount of opioid receptor activity in key areas of the brain, and there is an exaggerated hypothalamic pituitary adrenal axis activity in alcoholics in response to naltrexone, an opioid antagonist. In addition, relatives of alcoholics demonstrate higher levels of beta endorphin following alcohol, and in animals, a mu opioid receptor gene might be located near a QTL for alcohol preference in mice.

Neuropeptide Y is also of interest in the context of a low level of response to alcohol. This protein is mentioned here again to emphasize the fact that it is possible it functions

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independently of other domains of risk. The lecturer might choose to present the relevant material from Slide 12 here instead.

As is true with all of the slides outlined in this manual, individual lecturers will choose to emphasize one aspect more than another, and it is not envisioned that all slides will be used in all lectures.

Slide 17

OTHER POSSIBLE RISK MARKERS

EEG

**Corticotrophin Releasing
Factor (CRF)**

**Hypothalamic Pituitary Adrenal
Axis (HPA)**

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Other Possible Risk Markers

Other possible risk markers include several related to the background cortical EEG, and aspects of the system that includes corticotrophin releasing factor (CRF) and the hypothalamic pituitary adrenal axis (HPA). Several additional potentially interesting markers of risk might be discussed. While these are not explained in great detail here, the lecturer might choose to review any or all of the references outlined below. EEG findings of interest include a relatively low amount of slower alpha on the EEG in alcoholics and their relatives, a low voltage EEG in these same groups, and a variety of interesting aspects of CRF as well as the HPA axis. These markers might tie into increased predispositions through a low response to alcohol, independent psychiatric disorders, or via other mechanisms. However, it is important to emphasize that they might function as independent markers as well.

Slide 18

GENETIC INFLUENCES IN CONSEQUENCES

**Wernicke - Korsakov
Cirrhosis
Pancreatitis
Severe Withdrawal**

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Genetic Influences in Consequences

In addition to genetic factors that increase the overall risk for alcoholism, it is likely that additional genetic influences increase or decrease the risk for specific consequences of repeated heavy drinking among alcoholics. The purpose of this slide is to remind students that, as was emphasized in one of the first several slides of this lecture, genetic influences impact on the risk for a wide array of alcohol-related problems. Thus, some alcoholics might be at especially high risk for cirrhosis and/or pancreatitis, perhaps related to higher levels of acetaldehyde or other mechanisms. Other individuals might carry an enhanced risk for the Wernicke-Korsakoff's Syndrome secondary to a transketolase deficiency which makes them especially vulnerable to even modest decreases in thiamine.

Slide 19

IMPLICATIONS FOR PREVENTION

Enhance Education of Vulnerabilities

Find Environmental / Psychosocial Protective Factors Specific to Risk

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Implications for Prevention

Enhanced understanding of specific genetic vulnerabilities toward alcoholism might help identify subgroups of individuals for whom specific prevention techniques can be developed. If different individuals carry different types of predispositions toward and away from alcoholism, there might be specific environmental events that are more likely to exaggerate the impact of one mechanism of risk, while having little effect on another. Thus, it might be possible to study people who are carrying a specific mechanism of high risk and identify those who do not go on to develop alcoholism in order to identify environmental and other factors that helped minimize the risk. In addition, the identification of specific biological factors that increase the risk can be used as general education tools to demonstrate to people that the causes of alcoholism are complex, and that everyone needs to be aware of a potential risk, especially men and women with alcoholic close relatives.

Slide 20

IMPLICATIONS FOR TREATMENT

**Develop Rx for
Specific Risk Factors
Evaluate Rx Separately
in Subgroups**

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Implications for Treatment

Greater understanding of specific mechanisms of enhanced risk might identify alcohol-dependent individuals with different responses to a variety of treatments. The treatments for alcohol abuse and dependence are relatively generic and involve enhancing motivation, helping people to rebuild their lives without alcohol, and relapse prevention. While various medications have been identified which appear to contribute to recovery, their impact has generally been modest. It is possible that a greater understanding of the specific mechanisms of enhanced risk might allow for testing of specific treatments with an evaluation of how identified subgroups show greater or lesser intensities of response to the intervention. Thus, drugs like acamprosate (Campral) and naltrexone (Trexan or Revia) might be especially useful in subgroups of alcohol-dependent individuals.

Slide 21

SUMMARY

Genetic Influences Explain 60% of Risk

There are Several Different Genetic Influences

Relevant Phenotypes Relate to:

Alcohol Metabolism

Disinhibition / Impulsivity

Level of Reaction

Independent Psychiatric Disorders

Etc

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Summary

This summary slide emphasizes the major points made in the lecture.

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