VULNERABILITY FACTORS FOR ALCOHOLISM

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This is an exciting and challenging time in the search for genes that have impact on the risk for alcohol abuse and dependence (alcoholism). Family, twin, and adoption studies offer solid evidence that genetic factors contribute to the risk for severe and repetitive alcohol-related life problems, and at least 30 genetically influenced characteristics are being evaluated for their possible impact on the alcoholism risk (1–4). Similar to other complex genetic disorders, these risk factors are heterogeneous, and combine to explain an estimated 60% of the variance, often interacting with environmental forces that contribute to the remaining 40% (1–3). Complicating the search for specific genetic influences even further is the probability that most of the characteristics, or phenotypes, are themselves influenced by multiple genes, and the lack of precision of the definition of the broad phenotype, alcohol abuse, or dependence (1,4).

This chapter reviews the progress made during the 7 years since the publication of the previous edition (5) in the search for genes that influence the risk for alcoholism. Most of the genetic studies have used variations in two approaches described in more detail in Chapter 99, as well as in additional recent review articles (1,3,6). *Candidate gene studies* (also called case-control, association, or forward genetic investigations) begin with the hypothesis that a specific gene is related to the characteristic under study (7). If a limited number of multiple forms, or polymorphisms, of the gene are known, the proportion of individuals with and without the characteristic who have the specified polymorphism can be determined. Although this approach is an important step in identifying specific genes related to a phenotype, it is prone to false-positive results that occur if there are additional differences between groups with and without the characteristic (8). This problem, called population stratification, can be overcome by two variations of case-control studies where the relationship between the genetic marker and the characteristic, or phenotype, is evaluated among related individuals using a transmission disequilibrium or a haplotype relative risk approach (3,7).

The second and usually more labor-intensive technique is the *genetic linkage study*, or genome scan. This approach requires determining the presence of the phenotype and gathering blood for genotyping from either multiple generations of a large number of families or a large number of sibling pairs. The relationship between the phenotype and genetic signposts, or markers, across the 23 chromosomes is then evaluated. Unfortunately, genome scans are likely to identify only relatively powerful genes that explain a substantial proportion of the risk, and the data are best analyzed only when the mode of inheritance (e.g., dominant or recessive) is known. The potential linkage of a particular characteristic to a specific signpost helps identify areas of chromosomes of interest, after which more focused candidate gene analyses can be used to test individual genes near that marker.

This chapter describes some of the more promising results of the application of such approaches to alcohol use disorders, and briefly synthesizes the wide range of phenotypic and genotypic markers into a framework focusing on the several possible themes of potentially related characteristics described in Table 98.1. Reflecting space limitations, emphasis is placed on genetic factors relating to alcoholism, rather than to drugs in general; most studies focus on human rather than animal work; and review articles are often highlighted rather than a series of primary data sources.

TABLE 98.1. POSSIBLE BROAD FAMILIES OF RISK FACTORS

Level of response (LR)
P3/disinhibition/ASPD/type 2/B
Independent axis I disorders
Opioids
Alcohol metabolizing enzymes

ASPD, antisocial personality disorder.

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SOME SPECIFIC PHENOTYPIC AND GENETIC MARKERS OF INTEREST

Alcohol has impact on many neurochemical systems, whereas the use and consequences associated with this drug relate to many additional factors including personality traits, reinforcement, craving, and withdrawal symptoms (9,10). This panoply of phenomena has produced a wide range of hypotheses regarding how different phenotypes and candidate genes might contribute to the acquisition of drinking behaviors and the development of associated problems. Thus, judgment was needed to decide which potential phenotypic or genetic markers to highlight, and the reader is encouraged to turn to additional reviews (1,6,11–13). The information offered below is, somewhat arbitrarily, divided into results relevant to more broadly based phenotypes and those related to specific enzymes or genes.

Some Potentially Interesting Broad Phenotypes

A Low Level of Response (LR) to Alcohol

This characteristic, first proposed in 1975, reflects the need for higher doses of alcohol to produce an effect (1,10,14). The low LR to alcohol might enhance the probability of heavy drinking, encourage the formation of peer groups with similar drinking habits, and facilitate the acquisition of tolerance. LR is classically measured as the level of change in subjective feelings of intoxication, motor performance, hormone levels, and/or electrophysiologic measures observed at specific blood alcohol concentrations, but can also be evaluated by a self-report of the number of drinks required for specific effects (10,15,16). Low LRs are seen in about 40% of the estimated 700 children of alcoholics evaluated in the majority of the studies, and has been reported to characterize Native Americans, while high LRs and lower alcoholism risks have been noted for Jews and some Asian groups (17–25).

A longitudinal study of 453 20-year-old sons of alcoholics and controls showed that a low LR was a significant predictor of later alcohol abuse or dependence, explaining a significant proportion of the relationship between family history and alcoholism and alcoholic outcome in that sample (14,15). A 10-year follow-up of 64 sons of alcoholics and controls in Denmark found a significant relationship between less alcohol-induced physiologic changes and a high risk for alcohol abuse or dependence (26), whereas a 4-year follow-up of about 100 men and women found a relationship between a lower intensity of alcohol-induced incoordination and future alcohol problems for the men (27). Finally, a 10-year follow-up of almost 400 members of Australian twin pairs confirmed the relationship of the intensity of response to the alcoholic outcome for men (28).

The LR to alcohol is genetically influenced (29–33).

Studies in animals have identified quantitative trait loci (QTLs) associated with LR, and lower reactions to alcohol are often associated with higher alcohol intake (29,30). In humans, the LR is more similar in identical than fraternal twin pairs, and among first-degree relatives compared to unrelated individuals (28,32,33).

A candidate gene study reported additive relationships to LR for alleles for the γ-aminobutyric acid receptor Aα6 ($GABA_{A\alpha 6}$) and the serotonin transporter gene, whereas a separate sample revealed areas of potential linkages on chromosomes 1 and 21 (32,33). Additional candidate genes potentially tied to LRs include neuropeptide Y (NPY), neurotensin, adenylyl cyclase (AC) systems, protein kinase, aspects of serotonin (5-HT), and the hypothalamic-pituitary-adrenal (HPA) axis. However, a low LR appears to operate relatively independently of the event-related potential (ERP) and personality variables discussed in below, and is generally independent of alcohol metabolizing enzymes, but might crossover with some EEG characteristics (see below) (19,24,34).

Low Voltage or Low Alpha and EEGs

An overall low-voltage EEG pattern and a relative paucity of synchronized EEG waveforms appear to characterize a variety of conditions including anxiety and depression (6, 34,35). The importance of the EEG results reflects reports that alcohol increases alpha power, and that alcoholics might show lower amounts of alpha, higher beta activity, and/or lower voltage on the EEG overall (24,36). Such EEG patterns might have impact on the risk for alcoholism via several different mechanisms, including higher levels of anxiety.

Some children of alcoholics exhibit lower amounts of slower alpha and/or higher levels of faster alpha or beta EEG activity, and alcohol increases the proportion of slower alpha, whereas other offspring demonstrate lower overall EEG voltage (6,24,34–37). Finally, children of alcoholics demonstrate less intense, or shorter lasting EEG changes with alcohol, and there is a significant correlation between a low LR and EEG findings in the same subjects (24,34).

Evidence supporting genetic influences in EEG patterns includes greater similarities in identical versus fraternal twins, and a report of mendelian inheritance for slow alpha (38,39). Some relevant EEG characteristics might relate to genes on chromosome 20, although not all reports agree (40).

Impulsivity, the Antisocial Personality Disorder (ASPD), Types 2 and B Alcoholism

Conduct disorder (CD) in childhood and subsequent ASPD represent persisting patterns of impulsivity and difficulty benefiting from punishment, often associated with aggressive and criminal behavior. These disorders are potentially

related to personality characteristics of novelty- or sensation seeking, extroversion, neuroticism, and the absence of harm avoidance, attributes that might increase the risk for alcohol abuse or dependence (41). Related concepts that overlap with ASPD include type 2 and type B subgroups of alcoholics whose early onset and more severe course is often associated with criminality and dependence on other drugs (42, 43).

Almost two-thirds of people with ASPD are alcoholics, although only about 20% of alcoholic men fulfill criteria for this disorder (41–43). There is impressive familial crossover between CD/ASPD and alcoholism, and offspring of ASPD parents are likely to have a more severe alcoholic course (44, 45). Genetic factors are important in personality traits and some personality disorders, and ASPD and alcohol dependence are often inherited together (44–47).

ASPD (or CD) and substance use disorders might share the characteristic of neuronal disinhibition (41,48). The high levels of impulsivity and sensation seeking in CD and ASPD might, in turn, relate to aspects of 5-HT functioning, and/or to subtypes of GABA receptors (49,50). ASPD, or neuronal disinhibition, also appear to correlate with the ERP characteristic described in the next section (41), but neither ASPD nor the relevant ERP values correlate with a low LR to alcohol (19,51).

The P300 (P3) Wave of the ERP

The P300, or P3, is a positive polarity brain wave in the ERP paradigm observed approximately 300 msec after the presentation of an infrequent but anticipated stimulus (41, 48). Diminished amplitudes or shorter latencies of this wave reflect problems in attending and interpreting subtle environmental events (48,52,53). Low P3 amplitudes are seen in schizophrenia, major depressive disorder, attention-deficit/hyperactivity disorder (ADHD), and Alzheimer's disease (6, 52,53).

Adult alcoholics demonstrate small P3 waves even after extended periods of abstinence, although this might diminish with time (6,48,52). Although most investigators consider this a robust marker for adult alcoholism, a low amplitude P3 might more closely reflect states of temporary depression, a developmental delay, or aspects of CD or ASPD (41,52,53).

A relatively low amplitude P3 is seen in 20% to 35% of the offspring of alcoholics (6,48). A 4-year follow-up of 13 sons of alcoholics, 11 sons of nonalcoholics with family histories of alcoholism, and 12 family-history–negative controls revealed a relationship between a low P3 amplitude and delinquent behavior as well as subsequent substance use, although alcohol abuse and dependence were not directly tested (54). Another 8-year follow-up of 11 children of alcoholics and nine controls revealed lower P3 amplitudes for those four subjects who went on to develop an alcohol use disorder (55). Although neither of these investigations

controlled for the potential impact of CD and ASPD, the results are consistent with the relationship between P3 amplitude and the alcoholism risk.

As is true of many electrophysiologic measures, P3 amplitudes are genetically influenced (56,57). Data supporting these conclusions come from twin investigations, family studies, and a genetic linkage study that highlighted findings on chromosomes 2, 5, 6, and/or 13.

There are several interesting potential crossovers between P3 amplitude and other phenotypic or genetic markers of the alcoholism risk (19,52,53). Some investigators believe that most of the variance explained by P3 relates to CD or ASPD, or that finding might reflect activities of several dopamine (DA) receptors, which, in turn, might be related to impulsiveness or CD (41,52,53,58). At the same time, groups demonstrating low LRs to alcohol do not appear to have smaller P3 waves (19,51).

Independent Major Psychiatric Disorders

Alcoholics have an elevated risk for several major psychiatric disorders (59). For some people the psychiatric symptoms are likely to be temporary manifestations of intoxication and withdrawal, and for others alcohol problems might develop in the context of poor judgment and loss of control during major psychiatric syndromes (60,61). With schizophrenia, bipolar manic depressive disease, and ADHD, poor judgment, feelings of alienation, and high impulsivity might increase the chance of repeated heavy drinking (62–64).

The anxiety disorders are a series of syndromes with different clinical symptoms (in addition to anxiety), divergent treatments, and potentially different etiologies (65,66). Even after controlling for the potential impact of temporary substance-induced disorders, at least two anxiety syndromes—panic disorder and social phobia—appear to be tied to alcohol dependence, whereas some others, including obsessive-compulsive disorder, are not (65).

Each of the independent major psychiatric disorders listed above is likely to be genetically influenced (66). Most have abnormalities related to the HPA axis and to neurochemical systems including DA (especially relevant to schizophrenia), 5-HT (most closely tied to schizophrenia, anxiety, and mood disorders), norepinephrine (NE) and GABA (each tied to panic and mood disorders), and NPY (in anxiety) (66). Thus, as discussed below, genes related to the relevant psychiatric disorders might indirectly increase the risks for alcoholism through the clinical manifestations of the syndrome. However, these disorders might act independently of LR (14).

The Hypothalamic-Pituitary-Adrenal (HPA) Axis

Cortisol, adrenocorticotropin hormone (ACTH), corticotropin-releasing factor (CRF), prolactin, and related hormones are important in physiologic well-being, mood, anxi-

ety, aggression, and reactions to stress, including alcohol withdrawal (66–70). Aspects of HPA functioning might relate to an alcoholic predisposition in any of several ways. These include a possible contribution to a low LR, reflections of the actions of neurotransmitters such as 5-HT or DA in the course of some psychiatric disorders, and via the opioid system.

Some alcohol-dependent men and women have high cortisol, and children of alcoholics have a differential hormonal response to alcohol, opioid antagonists, and other challenges when compared to controls with some persisting after abstinence (67,68). Although there is some evidence that recovering alcoholics and children of alcoholics show lower levels of HPA response to alcohol, these same groups might show higher levels of response to naltrexone, an opioid antagonist (67–69).

The functioning of the HPA axis is at least partially under genetic control (70). Thus, activity of this system might contribute to the alcoholism risk, perhaps indirectly through several channels described in other sections.

Other Potentially Interesting Broad Phenotypes

Additional phenomena, including other personality disorders (e.g., borderline personality disorder), additional clinical characteristics (e.g., deficiencies in neuropsychological functioning), and other psychiatric syndromes [e.g., post-traumatic stress disorder (PTSD) or generalized anxiety disorder] have also been hypothesized to be related to the alcoholism risk (6,11,71).

Thus, reflecting space constraints, this discussion is not exhaustive and the reader should consider additional review papers.

Specific Proteins and Candidate Genes Potentially Related to the Alcoholism Risk

This subsection highlights some specific genes, enzymes, and other proteins that might relate to an alcoholism vulnerability. The distinction between broad potential phenotypic markers of alcoholism (discussed above) and the more specific markers noted here is somewhat arbitrary, but might be heuristically useful.

Adenylyl Cyclase (AC) and G Proteins

These proteins include three membrane-bound components of receptors, G (or guanine nucleotide binding) proteins, and the AC enzyme that are part of a complex second messenger system that translates the impact of alcohol, neurotransmitters, and other substances on the cell membrane or receptors into changes within the cell (72,73). The G proteins facilitate the coupling of at least nine different isoforms

of AC to cell membrane-bound receptors, which in turn affects production of 3′,5′-cyclic adenosine-monophosphate (cAMP), with the latter often used as a measure of the system's activity. This complex is affected by several neurotransmitters, and has impact on a variety of actions within the cell, including gene expression, and might impact on a variety of psychiatric disorders, including depression. G proteins come in several forms that either stimulate (G_s) or inhibit (G_I) the process.

Although results can differ when platelets or lymphocytes from patients or cells *in vitro* are used, alcohol appears to stimulate G_s. Recently detoxified alcoholics and their nonalcoholic relatives might have lower cAMP production following chemical stimulation of platelets or white blood cells, results that have been hypothesized to be related to a reduced G_s binding (72,74). However, AC activity is also affected by drinking and by withdrawal, and differences from controls can change depending on periods of abstinence or following the production of multiple generations of lymphocytes in cell culture (73,75). In the final analysis, differences between alcoholics and controls are probably both state and trait phenomena.

Regarding the latter, activity of the system appears to be genetically influenced, and it is possible the divergence in AC functioning is especially prominent in alcoholics with family histories of this disorder (75). The production of cAMP in chemically stimulated cells has also been investigated in children of alcoholics who might share lower levels of G_s-protein–stimulated cAMP production, especially if they have multiple alcoholic relatives (72,76).

One theory attempting to integrate these findings is that an avenue of alcoholism risk might be a low innate activity of the G_s system, with acute alcohol causing a temporary stimulation, after which abstinence from alcohol produces the opposite effect, which might lead to more alcohol intake in an attempt to compensate (77). The underlying difference has been hypothesized to involve a reduction of gene expression of the α subunit of the G_s protein (72). The process might have an impact on the development of tolerance, and, perhaps, the need for higher levels of alcohol to have an effect. Another mechanism is suggested by findings regarding the role of alcohol in decreasing neuronal excitability through enhancing G-protein–coupled inwardly rectifying potassium channels (GIRKs) (78). Perhaps these results might also tie into the actions of protein kinase and the effects of other markers such as NPY, as well as through additional neurochemical systems such as 5-HT (79,80).

Protein Kinase C (PKC)

These proteins encompass at least three families of enzymes that, similar to AC, have important functions in translating the effects of neurotransmitters on receptors into the cell. These calcium-activated, phospholipid-dependent proteins are widely distributed in the body, and function by phos-

phorylating target proteins, including G proteins, and thus, mediating changes in intracellular signaling (81,82).

The direction of the impact of alcohol on PKC activity can be different with acute versus chronic administration, but in general ethanol affects the movement of this protein from the area around the nucleus to the cytoplasm (83). The changes in PKC subsequently have impact on the actions of several neurotransmitter receptors, including 5-HT and GABA$_A$, and thus, are likely to affect alcohol intoxication and tolerance.

Alcohol-dependent individuals may have higher amounts of PKC-ϵ, a form that might inhibit the actions of GABA$_A$ receptors, possibly tying PKC-ϵ to a low LR to alcohol (82). Although no data are yet available in children of alcoholics, mice genetically engineered for an absence of PKC-ϵ have both a high sensitivity to alcohol and lower self-administration of this drug (82). Such animals also show a decreased reaction to pain, perhaps reflecting changes in opioid activity (84). There is additional evidence that PKC-ϵ knockout mice have a lower intensity of reaction to alcohol, and less ability to develop tolerance to at least some effects of the drug (81).

Neuropeptide Y (NPY)

NPY is a widely distributed neurotransmitter that affects multiple receptor subtypes including Y1 (in the amygdala where NPY decreases feelings of anxiety), and Y5 (in the hypothalamus where NPY might increase appetitive behaviors) (79,85). NPY appears to act through G proteins, producing an inhibition of AC production, and this transmitter can facilitate the release of DA in the nucleus accumbens (86). It has been hypothesized to play a role in eating disorders, depression, anxiety, and the actions of opioids (87).

Acute alcohol intake has impact on NPY release, which in turn affects the release of DA, possibly contributing to some rewarding effects of alcohol or adding to some psychiatric symptoms (85,86,88). Chronic alcohol intake and withdrawal are associated with increased NPY in the hypothalamus, and increased responsiveness of CRF to NPY (85).

Alcohol-preferring rats have a QTL on chromosome 4 [logarithm of odds (LOD) = 8.6], which explains about a third of the enhanced alcohol intake, and which is located in an area where NPY has been mapped (89). In addition, rats bred to consume high levels of alcohol have increased NPY activity in the amygdala (perhaps reflecting levels of anxiety), along with decreased NPY in the frontal cortex and hippocampus (perhaps reflecting a lower level of satiety) (85,88). Mice genetically engineered for an absence of NPY drink more alcohol and have a lower intensity of response compared to wild-type mice, whereas transgenetic mice with increased NPY have less alcohol consumption and higher responses to alcohol (79,90). Studies have not yet been carried out in alcoholics or their offspring.

Opioid-Like Substances, Including β-Endorphin

The opioids are endogenous proteins, including endorphins and enkephalins, as well as most of the prescription pain medications, methadone, heroin, codeine, and morphine, each of which bind to opioid receptors. Their actions diminish pain, decrease respirations, cause euphoria, and produce a decreased motility in the gut. There are a variety of opioid receptor subtypes including μ, κ, and δ, with μ most closely tied to analgesic and reinforcing effects (91). Opioids have impact on DA, 5-HT, and NPY activity, and relate to some psychiatric disorders, such as depression (92).

Acute alcohol intake results in the release of endogenous opioids, and stimulates relevant receptors (6,93). Aspects of tolerance and withdrawal from alcohol might relate to changes in functioning of the μ receptors, and alcohol-preferring animals have an increase in these receptors in the ventral tegmentum, along with a greater increase in β-endorphin following alcohol (94–96). An exaggerated HPA response to naltrexone (an opioid antagonist) has been reported in alcoholics and their relatives, perhaps reflecting less baseline opioid functioning (97). Decreased β-endorphin has been noted in the cerebrospinal fluid (CSF) of abstinent alcoholics, and their relatives demonstrate more release of β-endorphin following alcohol (94,96). Opioid antagonists, such as naltrexone and nalmephene, can decrease the self-administration of alcohol in animals and humans, perhaps by blunting the stimulatory effect of alcohol, enhancing the sedative effects of this drug, and/or through decreased levels of reinforcement from alcohol (93,97,98). A μ opioid receptor gene might be located near a QTL for alcohol preference in mice (99), and there is a possible association between alcoholism and some of the six more known alleles of the μ opioid receptor (OPRM1), although not all studies agree (6,94,100).

The Serotonin (5-HT) Systems

The actions of this neurotransmitter, which are mediated through the 5-HT transporter (5-HTT) and more than 14 different receptors, affect HPA functioning, anxiety, impulsivity, eating behaviors, depression, and other conditions (6). Numerous drugs of abuse have impact on 5-HT systems, including alcohol, and 5-HT, in turn, also interacts with other neurotransmitters, especially DA (6). The following data suggest that different genes affecting 5-HT levels could increase the alcoholism risk through several different mechanisms.

5-HT agonists can simulate signs of intoxication, and, perhaps, feelings of craving (101). Alcoholics, especially those with aggressiveness or an early onset of their substance use disorder, may have lower levels of platelet and brain 5-HT, diminished responses to 5-HT boosting drugs, and lower levels of 5-HT metabolites in the CSF (6,102). Treatment with drugs that boost 5-HT in the synapse [e.g., selec-

tive serotonin reuptake inhibitors (SSRIs)], produces a modest decrease in voluntary alcohol intake in animals and humans (6).

Alcohol preference in animals is associated with a QTL near the genes encoding for the 5-HTT (103). The s-allele may relate to nervousness, harm avoidance, and other forms of anxiety that might tie in to axis I anxiety disorders and more severe alcohol withdrawal, although not all authors agree (49,104). The l-allele, which might produce a protein that more rapidly takes up 5-HT from the synapse, has been tied to a low LR to alcohol and an enhanced alcoholism risk (32). Another gene that controls the production of the rate limiting enzyme in the synthesis of 5-HT, *tryptophan hydroxylase*, might also relate to lower 5-HT levels and more impulsiveness, suicidality, as well as a predisposition toward alcoholism (105).

Genes for some 5-HT receptors might be associated with higher alcohol intake either directly or through ASPD, depressive disorders, schizophrenia, or anxiety disorders. Findings include a high receptor density for 5-HT$_{1A}$ or a decrease in 5-HT$_{1B}$ activity in alcohol-preferring rats, with 5-HT$_{1B}$ knockout mice demonstrating higher levels of alcohol intake (106,107). Turning to a second family of receptors, there is evidence of a decrease in 5-HT$_{2C}$ receptor sensitivity in alcoholics, along with a potential increase in the density of these proteins in the hippocampus in alcohol-preferring rats (108). A third family has also been implicated through the actions of the 5-HT$_3$ receptor, which promotes the release of dopamine in the nucleus accumbens in the context of alcohol (6,109).

Children of alcoholics might have more rapid uptake of 5-HT in platelets, perhaps indicating a lower level of 5-HT in the synapse that might relate to LR (110). This is consistent with lower LR to alcohol in the offspring who have the l-allele of the 5-HTT (32). Finally, a drug that antagonizes activity of the 5-HT$_3$receptor, ondansetron, both decreases subjective feelings of intoxication with alcohol and decreases alcohol intake in alcoholics and their relatives (109).

The Potential Importance of Dopamine (DA)

This neurotransmitter has broad effects in the brain, including in the mesolimbic system where it functions as a mediator of reward or pleasure (6,111). DA impacts on the risk for heavy drinking and alcoholism through potentially diverse mechanisms including the reinforcing effects of the drug, personality characteristics, and via several psychiatric disorders.

Ethanol causes the release of DA in the mesolimbic system, affects DA neurons in the ventral tegmentum, and the reinforcement from alcohol decreases when DA antagonists are given (6,111,112). There might be a general decrease in overall DA functioning among more violent alcoholics, as evidenced by lower levels of DA metabolites in the CSF,

and DA activity might also relate to personality characteristics such as novelty seeking and to ASPD (113,114).

These findings have led to a search for specific DA markers possibly tied to a vulnerability toward alcoholism. A decrease in the D2 receptor density has been reported in the brain of alcohol-preferring rodents and some alcoholics, as has a blunted hormonal response to D2 agonists, at least soon after withdrawal (115,116). Lower levels of DA in the synapse might result from a higher density of DA uptake as seen in alcohol-preferring primates, although possibly reflecting withdrawal, the opposite was reported in the striatum in a small sample of nonviolent alcoholics (116,117).

Although it is not clear whether they are functional, several alleles of the Taq1A marker for the D2 DA receptor (DRD2) have been reported to be linked to alcoholism, especially severe early-onset problems, and thus possibly to ASPD (6,118). However, results relating to this candidate have not been replicated in genome scans, and there are as many nonconfirmatory studies as there are positive ones (6, 119). Additional interest has been expressed regarding the D4 receptor and several alleles of the DA transporter, but with conflicting results (120,121).

GABA, Norepinephrine (NE), and Monoamine Oxidase (MAO)

This subsection briefly reviews several markers that might relate to the alcoholism risk. GABA, a ubiquitous inhibitory neurotransmitter, has an important role in several conditions possibly related to the alcoholism risk including anxiety, mood disorders, schizophrenia, and aggressive behaviors (32,66). There are multiple GABA receptors, with special interest for alcohol intoxication or withdrawal for the estimated 13 or more subunits for the GABA$_A$ receptor complex (6,32,122). Alcohol-dependent men and women have a decreased density of GABA$_A$ receptors, and might show decreased responses to lorazepam in frontal brain regions and in the basal ganglia, while demonstrating abnormal responses to a benzodiazepine antagonist flumazenil (123, 124). A diminished response to brain depressants might occur with a common mutation of the GABA$_{A\alpha6}$ receptor, which might also reflect a low LR to alcohol (32,122). In addition, a possible predisposition toward alcohol dependence might link to an area of chromosome 4 near genes noted to have an impact on GABA functioning (32,125).

Monoamines, including 5-HT, NE, and DA, are metabolized in part by MAO. Alcoholics, especially those with concomitant ASPD, might demonstrate low MAO activities, perhaps reflecting alternate forms of genes, although this finding might be an artifact of recent smoking (126).

Finally, alcoholics, especially those with multiple alcoholic relatives, might have a blunted hormonal response to drugs that have impact on NE, especially during withdrawal and early abstinence (127). Thus, NE might also increase the alcoholism risk through vulnerability for panic and other anxiety disorders.

Alcohol-Metabolizing Enzymes

The best-documented genetic factors related to alcoholism involve genes controlling the two prominent alcohol-metabolizing enzymes, alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH). As discussed in Chapter 99, Asian men and women who lack the low k_m, mitochondrial ALDH (i.e., have the homozygous ALDH2-2, 2-2 genotype) and who, thus, produce very high levels of the first breakdown product of alcohol (acetaldehyde), have almost no risk for alcohol dependence (11,12,128). Heterozygotes with the ALDH2-1, 2-2 genotype produce higher acetaldehyde levels than Asians with ALDH2-1, 2-1, and have an enhanced level of response to alcohol and lower risk for alcoholism. For ADH, individuals carrying the genotypes that are associated with more rapid metabolism of alcohol (e.g., those with ADH2-2, 2-3, or 3-1 alleles) more rapidly produce acetaldehyde and have a diminished alcoholism risk, especially if these genotypes are associated with the relevant ALDH markers described above (129,130). The ADH enzyme forms appear to exert less influence on the alcoholism risk, but are applicable to a broader range of ethnic and racial groups.

Thus, ADH and ALDH enzyme patterns have several potential mechanisms associated with an altered risk for alcohol dependence. These include an aversive reaction to alcohol related to very high levels of acetaldehyde in ALDH2-2 homozygotes, whereas individuals who are het-

erozygotes for ALDH2-2 and those with more rapid metabolism of alcohol through ADH forms might decrease their risk through an increased intensity of reaction to alcohol, not necessarily an overall more aversive response (25).

AN ATTEMPT TO SYNTHESIZE THESE DATA

Background

This chapter has briefly reviewed many genetically influenced characteristics that may be relevant to the alcoholism risk. However, it is unlikely that there are 30 or so independent genetically influenced trait markers for alcoholism, and thus the findings are likely to represent a more limited number of overarching phenomena, or families of risk factors.

As in the selection of markers of interest, the identification of possible families of findings, or domains, requires subjective judgment. Initially, I was tempted to highlight a separate domain for 5-HT and another for DA markers, and I recognize that it is possible that the functioning of the HPA axis might be a core mediator of risk by itself. However, I believe that most of these markers might function as correlates of several different mechanisms through which broader domains of influence operate. Therefore, I propose that the majority of the genetically related markers of the alcoholism risk might fall into about five relatively independent overarching categories (Table 98.1). The specific markers are summarized in Table 98.2.

TABLE 98.2. POSSIBLE FAMILIES OF RISK FACTORS

	LR	Disinhibition	Axis II	Opioids	ALDH/ADH
Broad markers					
EEG alpha	X		X		
Voltage	X		X		
HPA	X		X	X	X
5-HT levels		X	X	X	
DA levels		X	X	X	
Neuropsychiatric		X	X		
Genes/proteins					
AC	X		X		
G protein	X		X		
PKC	X			X	
NPY	X		X	X	
5-HT$_{1A/1B/2C}$	?	?	?		
5-HT$_3$	X				
5-HTT	X	X	X		
TOH		X	X		
DRD2		X			
D4		X			
DAT		X			
GABA$_A$	X	X	X		

AC, adenylyl cyclase; ADH, alcohol dehydrogenase; ALDH, aldehyde dehydrogenase; DA, dopamine; DAT, dopamine transporter; DRD2, dopamine receptor D2; GABA, γ-aminobutyric acid; HPA, hypothalemic-pituitary-adrenal axis; 5-HT, serotonin; LR, level of response; NPY, neuropeptide Y; PKC, protein kinase C.

A Domain Related to a Low LR to Alcohol

A low LR is a useful place to begin to demonstrate how some of the literature might be synthesized. Although the central aspect of this family of findings might be altered 5-HT or HPA axis functioning, it is equally plausible that a low LR to alcohol is the characteristic that pulls together the other findings.

Theoretically, a low LR to alcohol might reflect the final phenotypic path through which many different markers operate. Dampened responses to alcohol in children of alcoholics have been observed for several hormones, electrophysiologic measures, subjective feelings of intoxication, and motor performance. This array of findings might reflect altered second messenger and intracellular signaling actions that are less sensitive to alcohol-induced neurochemical changes, including genes that affect G proteins, AC, and PKC. Other mechanisms that might independently affect the LR to alcohol might include genes that have impact on NPY, GABA, 5-HT, and DA. The subsequent diminished effect of alcohol on neurons might also function to produce less change in the EEG and HPA axis responses, thereby helping to mediate the reaction to alcohol overall (24,67).

Other components of some of these same systems, including DA, 5-HT, DA, and HPA functioning, are also likely to function through additional mechanisms as mediators of several other domains of risk factors. For example, alternative aspects of these systems might have impact on disinhibition, independent psychiatric disorders, and opioid system functioning. As discussed further below, most of those additional attributes are likely to be distinct from those that relate to a low LR. It is hoped that the identification of specific genes linked to LR will help pinpoint which of these neurochemical systems contribute most to this domain.

A Domain Encompassing Disinhibition, a Low P3 Amplitude, ASPD, and Early-Onset and More Severe Subtypes of Alcoholism

A low P3 amplitude of the ERP and aspects of CD and/or ASPD characterize a substantial minority of young children of alcoholics; aspects of this domain are genetically influenced, and these phenomena relate to the future alcoholism risk. Although low LR appears to be relatively specific for the alcoholism risk (19,24), the disinhibition domain might enhance the risk for all substance use disorders (41,48,52). Theoretically, these markers might be associated with poor judgment and impulsive behavior, which both increase the risk for ingesting substances and for problems learning how to control their use.

This potential domain appears to operate independently of a low LR and alcohol-metabolizing enzymes, and there are few data that would link these phenomena to the opioids

and major axis I psychiatric disorders (14,53). It is possible that one childhood psychiatric disorder, ADHD, might also fit into the disinhibition domain, and other investigators might believe that some anxiety disorders might fit here as well.

A number of neurochemical markers described above might fit together under a general heading of disinhibition. These include several DA-related genes (e.g., DRD2, and DRD4 receptors), the DA transporter, and aspects of the DA function tied to sensation seeking, novelty seeking, as well as early-onset and severe alcoholism (6,58). Aspects of 5-HT might also be relevant, with the major finding here (as opposed to the LR domain where only the 5-HTT might contribute) being low 5-HT functioning overall, and genes having impact on tryptophan hydroxylase (6,102). Several additional findings that are discussed in more detail in other publications might also apply to this domain, including cognitive difficulties with executive cognitive functioning, which might cross over with CD, ASPD, and the substance use disorders.

Independent Axis I Major Psychiatric Disorders as a Potential Domain of Risk

The central hypothesis for this domain is that genes that contribute to the development of some psychiatric disorders might indirectly increase the risk for heavy drinking and alcohol-related problems. The axis I disorders most closely tied to an elevated alcoholism risk are schizophrenia and bipolar manic depressive disorder as described above (60, 61,64). An enhanced alcoholism risk might also be associated with panic disorder and social phobia, and possibly PTSD or generalized anxiety disorder. Each relevant condition is itself a complex genetic disorder, with separate, but perhaps overlapping, sets of genes. Furthermore, it is possible that different environmental events add to or detract from the risk for each of these conditions.

For this discussion, it is not essential to determine if the individual with schizophrenia, for example, is drinking to decrease the symptoms of their underlying and independent disorder (although this contention is not well supported) (63,131), or if the problems were a result of the combination of poor judgment, a large amount of free time, and living in a heavy drinking environment. In either case, the search for genetic factors in alcoholism might be more efficient if the potential impact of genes related to these independent disorders is considered. Once genetic markers for an additional characteristic (such as LR) have been found, they can be tested in these more complex subjects to determine whether it adds further to the risk.

The core characteristics of this domain might only indirectly relate to independent psychiatric disorders. It is possible that the predispositions toward both alcoholism and a

psychiatric disorder might operate through the same genes that have impact on the 5-HT, DA, or the HPA systems. Or the relationships could reflect transmission disequilibrium for the genes having impact on the alcoholism risk and those related to some of the psychiatric disorders. The answer to these questions might be more easily addressed once specific genes linked to the alcoholism risk and those linked to the relevant independent psychiatric disorders have been identified.

A Possible Domain Related to the Opioid System

A low level of activity of endogenous opioids could alter the intensity of reinforcement from alcohol (93,94). The markers reported above, as well as characteristics potentially related to the opioid systems, might form a domain that appears to be relatively independent of other risk factors. The decision to place opioids in a separate family of findings rests with evidence of high levels of alcohol dependence among opioid-dependent individuals, the closer than expected relationship between alcohol and opioid consumption in animals, and my subjective judgment that opioid systems are likely to function primarily as a characteristic subsumed under a separate global domain.

There is crossover between this hypothesized domain and the functioning of the HPA axis, and 5-HT, DA systems. Thus, it is possible this is not a separate domain of influence, but the possibility of a relatively unique impact is worth considering.

The Importance of Alcohol-Metabolizing Enzymes

Both the genetic control and the impact on drinking behaviors for alcohol-metabolizing enzymes have been well established (18,128). The risk for alcohol dependence among individuals with the ALDH2-2, 2-2 genotype is close to zero. ALDH2-2, 2-1 heterozygotes have significantly lower levels of risk as, apparently, do some people who have the more efficient ADH2-2, 2-3, and 3-1 alleles. The mechanisms through which the relevant genes are likely to operate include an aversive effect of alcohol at high acetaldehyde levels (as seen with ALDH2-2 homozygotes), and possibly through an enhanced LR to alcohol (for ALDH2-2, 2-1 heterozygotes and the relevant ADH alleles).

Despite some crossover with LR for ALDH heterozygotes, it is likely that the alleles controlling these alcohol-metabolizing enzymes operate as a relatively separate domain of risk. Few, if any, data tie these alleles to disinhibition or axis II major psychiatric disorders, and a strong link to opioid systems seems unlikely. However, it is possible that some of the impact of acetaldehyde might operate through elevations in HPA hormones, and the accompanying neurochemical changes might have impact on second messenger or other intracellular signaling systems.

CONCLUDING REMARKS

During the 7 years since publication of the previous edition, there have been exciting developments regarding the study of complex genetically influenced disorders. Progress in the studies of the genetic factors in alcohol dependence has been important because this is one of the most prevalent major psychiatric conditions, and is associated with substantial morbidity and mortality.

Some readers will be most interested in the citations from publications over the prior decade regarding the broad phenotypic or more focused genotypic markers described here. It is also hoped that some will also benefit from considering the hypothesis that many of these markers of risk can be grouped together into overarching phenomena including a low LR disinhibition, independent axis II psychiatric disorders, the opioid system, or alcohol-metabolizing enzymes.

The idea of searching for central themes among the markers is potentially more important than whether any of the hypothesized domains survive the test of time. It is possible that several of the families of findings discussed here would have been better subsumed under changes in the HPA axis, that findings related to specific neurochemical systems might each represent separate domains of influence, and that some of the hypothesized domains might be epiphenomena operating under the umbrella of genes that affect the levels of functioning in specific neurochemical systems. However, as is true of all fields of science, it is important to outline possible examples of a generic approach, in the hope of stimulating additional research to determine the most appropriate domains of influence.

ACKNOWLEDGMENTS

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