
Gene Variability and Vulnerability to Alcoholism

JOHN J. DORIA, M.S.

Variability within genes may explain why so many differences in alcoholism exist between individuals and among populations. Researchers studying this phenomenon have focused on genes that may affect both the way the body metabolizes alcohol and the way the brain responds to alcohol, thereby increasing or decreasing the likelihood of addiction. Gene variants may ultimately be used as markers of alcoholism vulnerability and as guides to help match patients to the most appropriate alcoholism therapies. **KEY**

WORDS: gene; AOD use susceptibility; AOD dependence; metabolism; neurotransmitters; receptors; dopamine; serotonin; endogenous opioids

Evidence for the familial transmission of alcoholism has stimulated researchers to search extensively for specific genes that may confer vulnerability to alcoholism. Genetic analysis of behavioral disorders such as alcoholism is, however, especially difficult. Unlike single-gene disorders such as Huntington's disease,¹ behavioral traits appear to be influenced by the interaction of several genes, each of which may exert only a small effect (Plomin 1990). Social, cultural, and other nongenetic influences interact with genetic vulnerability to cause alcoholism (Devor 1993).

Despite the importance of nongenetic influences, however, the disease of alcoholism always occurs within a matrix of genetically determined mechanisms that differ between individuals and between populations. The basis for these differences is polymorphism, the existence of one or more variant forms (i.e., alleles) of the same gene. These inborn genetic differences serve as a starting point for understanding the web of interactions that lead to alcoholism (Goldman 1995).

Various methods exist for testing the contributions of individual genes to alcoholism vulnerability; these methods are described in other articles in this issue (see the Tools of Genetic Research section, beginning on page 190). Researchers have focused their attention on genes that may

affect the way the body processes (i.e., metabolizes) alcohol and the way the brain responds to alcohol to increase or diminish the potential for addiction (Froehlich 1995).

GENES FOR ALCOHOL METABOLISM

Alcohol is metabolized in the liver by two enzymes acting sequentially. First, alcohol dehydrogenase (ADH) converts alcohol to a chemical called acetaldehyde. Acetaldehyde, in turn, is converted to acetate by aldehyde dehydrogenase (ALDH) (Goldman and Enoch 1990). Acetaldehyde is a toxic substance that may be partially responsible for some of the adverse medical consequences of alcohol consumption (Lieber 1994).

After consuming alcohol, certain Asian populations experience facial flushing, palpitations, headache, dizziness, and nausea. The flushing reaction is associated primarily with a defective variant of ALDH that allows the accumulation of acetaldehyde in the blood and tissues after alcohol consumption (Thomasson et al. 1993). In addition, researchers have detected an ADH variant that metabolizes alcohol at an increased rate, thereby contributing to acetaldehyde buildup. Although either enzyme variant can cause the alcohol flushing reaction, their effects are also

additive (Thomasson et al. 1993). These effects are believed to deter drinking among those who experience them.² Scientists have studied *ADH* and *ALDH* alleles extensively in various populations. (For a review, see the article by Wall and Ehlers, pp. 184–189.)

GENES RELATED TO NERVE CELL COMMUNICATION

All brain activity results from communication between nerve cells. Alcoholism researchers have concentrated on the pathways of nerve cell communication most likely to assist in regulating alcohol consumption and promoting alcoholism. Among these are pathways that use the neurotransmitters³ dopamine and serotonin as well as the endogenous opioids.

Dopamine

Dopamine is a neurotransmitter whose many functions include facilitating learning and motivation, processes that are

²Cultural factors also contribute to differences in drinking patterns between populations.

³Communicating nerve cells generally are separated by a microscopic gap called a synapse. Nerve cells release molecules called neurotransmitters into the synapse, where they bind to receptor proteins in the walls of other nerve cells and thereby carry messages from cell to cell.

¹For a definition of this and other technical terms used in this article, see central glossary, pp. 182–183.

JOHN J. DORIA, M.S., is a science editor for Alcohol Health & Research World.

central to developing addiction to alcohol and other drugs (AOD's) (Di Chiara 1995).

Dopamine Metabolism. Dopamine released into a synapse binds rapidly to its receptors and is transported quickly back into the nerve cell that released it (i.e., reuptake). Following reuptake, some dopamine is stored for subsequent rerelease; the rest is metabolized by the enzyme monoamine oxidase (MAO). This enzyme occurs in two forms, or isoenzymes: MAO-A and MAO-B, which are encoded by two similar but distinct genes located close together on the same chromosome.

The precise roles of the two isoenzymes have not been fully clarified, although both MAO-A and MAO-B can metabolize dopamine. Lowered MAO-B activity has been detected frequently among alcoholics and their close relatives, compared with higher MAO-B activity among nonalcoholics. This difference could be attributed to polymorphism within the *MAO-B* gene. Such polymorphism may represent variation in the DNA sequence that codes for the enzyme's structure or in the DNA sequence that regulates the gene's activity (Devor et al. 1993). In either case, if variation in MAO-B activity can be related to specific DNA sequence variation within the *MAO-B* gene, the altered DNA sequence might serve as a genetic marker to help identify persons at risk for alcoholism (Devor et al. 1993).⁴

Dopamine Receptors. Five types of dopamine receptors have been identified in the brain and have been designated D₁ through D₅. Although all five receptors respond to dopamine, their specific properties and functions differ slightly from one another (Mansour et al. 1995). The dopamine receptor D₂ plays a role in reinforcement, a key component of the process by which a behavior, such as alcohol consumption, becomes habitual (Di Chiara 1995). In 1990, Blum and colleagues reported a strong population association⁵ between alcoholism and a specific allele (A1) of the gene that directs the synthesis of D₂ (the gene is known as *DRD₂*). Specifically, researchers observed allele A1 of *DRD₂* more frequently in a group of alcoholics compared with a group of nonalcoholic subjects (i.e., controls) (for a discussion of

population association methods, see the article by Goate, pp. 217–220).

Subsequent research found this population association to be much weaker than originally reported (Parsian et al. 1991; Blum et al. 1991, 1993) or failed to find an association at all (Goldman et al. 1992, 1993; Gelernter 1993; Cook et al. 1992). In addition, Gejman and colleagues (1994) examined the DNA sequence of *DRD₂* from large samples of alcoholics and schizophrenics and detected no variation in the coding segment of the gene that could account for an association with alcoholism.

Spurious results in population association studies may result from failure to match test subjects adequately to controls for ethnicity or other factors that may affect overall genetic composition. Significantly, in this regard, studies conducted in ethnically well-defined populations have generally failed to show an association between *DRD₂* and alcoholism (Goldman et al. 1992; Arinami et al. 1993). According to Goldman and colleagues (1993), differences in *DRD₂* polymorphism among diverse populations are sufficient to account for spurious population associations or, conversely, to obscure such associations that may exist.

Despite the failure to replicate the initial research on *DRD₂*, the central role dopamine plays in the addiction process ensures that research on dopamine receptor genes will continue. Researchers have reported associations between *DRD₂* and alcoholism-related phenomena (Comings et al. 1991), including drug abuse (Smith et al. 1992; Noble 1993) and aberrations of brain electrical activity (Noble et al. 1994). Variation also has been detected in the D₃ (Rietschel et al. 1993) and D₄ (Lichter et al. 1993) receptors, although the significance of this finding is unclear.

Serotonin

Many investigators believe that alcoholism is related to the levels in the brain of the neurotransmitter serotonin (Litten and Allen 1991). Serotonin helps regulate such functions as bodily rhythms, food and water intake, sexual response, and aggression. Brain serotonin concentrations, which are difficult to measure directly, can be estimated by measuring the concentration in cerebrospinal fluid (CSF)⁶ of 5-hydroxyindoleacetic acid (5-HIAA), a product of serotonin metabolism. Reduced brain serotonin function, as indicated by low CSF 5-HIAA concentration, is

associated with increased risk of violent behavior, suicide, depression, and alcoholism among people with psychiatric disorders as well as the general population (reviewed in Pihl and Peterson 1993). These manifestations appear to be causally related: The presence of one appears to increase the risk for any or all of the others (reviewed in Virkkunen and Linnoila 1993 and in Tollefson 1995). In addition, alcoholism and other problems involving impulsive behavior appear to be inherited together in families (Cloninger et al. 1985; Bohman 1978).

Family studies suggest that genetic polymorphism influences the function of serotonin and its receptors. Therefore, researchers are attempting to identify specific alleles that may influence vulnerability to alcoholism or behaviors that may be associated with alcoholism (Nielsen et al. 1994; Virkkunen et al. 1994a,b).

Genes for Serotonin Synthesis and Metabolism. Variations in serotonin levels and activity among different populations may be caused by polymorphism in genes that control serotonin synthesis and metabolism. Many of the genes potentially important in controlling serotonin metabolism have been cloned, including the gene that codes for the enzyme tryptophan hydroxylase (TPH) (Nielsen et al. 1994). TPH initiates the synthesis of serotonin from tryptophan, a chemical found in food. An allele of the TPH gene has been associated with low CSF 5-HIAA concentrations along with suicidal behavior among a group of alcoholic prisoners incarcerated in Finland for criminal offenses involving impulsivity (Nielsen et al. 1994). However, Abbar and colleagues (1995) did not find an association between TPH polymorphism and suicidal behaviors among patients in a French hospital.

MAO-A, discussed previously with respect to dopamine, also metabolizes serotonin. In a study of a single large family, researchers linked deficient enzymatic activity of MAO-A to a minor alteration in the DNA sequence of the *MAO-A* gene. Behavioral manifestations included borderline mental retardation, impulsive aggression, arson, attempted rape, and exhibitionism. This symptom cluster does not specifically include alcoholism and has not yet been reported in other populations (Brunner et al. 1993; Goldman 1995).

The genes for both MAO-A and MAO-B have been cloned (reviewed in Nielsen et al. 1994). However, both genes are on the female sex (i.e., X) chromosome. Because a high percentage of alcoholism is transferred from father to son, it is unlikely that genes

⁴Alternate explanations for differences in MAO-B activity have been postulated, some of which do not require genetic involvement.

⁵A population association indicates that a particular allele occurs more frequently in a group of subjects who have the disease, compared with a group of control subjects, who do not have the disease.

⁶Cerebrospinal fluid surrounds the brain and spinal cord and fills the cavities within the brain.

located on the X chromosome account for more than a small fraction of the genetic vulnerability to alcoholism; nonetheless, MAO-A and MAO-B gene polymorphisms could be involved in the genetic liability of a subgroup of alcoholics (Goldman 1995).

Also cloned are the gene for aromatic L-amino acid decarboxylase (Sumi-Ichinose et al. 1992), another enzyme involved in serotonin synthesis, and the gene for the serotonin transporter, a protein in the nerve cell membrane involved in serotonin reuptake (Hoffman et al. 1991). Effects on alcoholism of possible polymorphisms at these genes have not been established.

Genes for Serotonin Receptors.

Researchers have identified seven major classes of serotonin receptors, designated 5HT₁ through 5HT₇ (Grant 1995). These families have been further divided into subtypes, at least eight of which have been cloned (Goldman 1995). Receptor 5HT₃ plays a role in the acute and chronic effects of AOD's on the nervous system and also has been implicated in psychiatric illnesses such as schizophrenia, anxiety, and Alzheimer's disease (Grant 1995). When activated by serotonin, 5HT₃ functions to regulate communication along nerve cell pathways by influencing the release of certain neurotransmitters into synapses. Among the neurotransmitters regulated by 5HT₃ is dopamine, discussed previously. Researchers have suggested that the direct action of alcohol on 5HT₃ leads to increased dopamine activity in areas of the brain involved in reinforcement, potentially contributing to the development of addiction behaviors (Johnson and Cowen 1993; Grant 1995). Researchers are studying variations of other serotonin receptor genes for possible associations with alcoholism (Blanchard et al. 1992; Lappalainen et al. 1995).

Genes Related to Endogenous Opioids

Endogenous opioids are neurotransmitters in the human nervous system that produce effects similar to those of morphine and other opiates. Evidence suggests that alcohol-induced activation of the endogenous opioid system may affect alcohol reinforcement and drinking behavior (Froehlich 1995). This theory is supported by the effectiveness of naltrexone, an opiate antagonist, in helping prevent relapse in patients being treated for alcoholism (Volpicelli et al. 1992). Animal studies suggest that a genetic predisposition toward alcohol consumption may be accompanied by increased responsiveness of the

endogenous opioid system to alcohol (De Waele et al. 1992). In one study, alcohol consumption produced a significant increase in blood levels of beta-endorphin in subjects with significant family histories of alcoholism, but not in families without histories of alcoholism. The mechanism of this difference is unknown, although the results indicate that the basis of the difference is genetic (Gianoulakis et al. 1989).

CONCLUSIONS

The causes and manifestations of alcoholism may differ significantly among individuals. Apart from environmental influences, multiple genes may each contribute to the disorder, and some researchers have suggested that certain families may have their own unique mixture of genes responsible for alcoholism vulnerability (Plomin 1990).

Population and molecular biology studies among humans will continue to shed light on the disorder. Animal studies will provide additional evidence, for example, by mapping quantitative trait loci (QTL), genes that together contribute to an effect although their individual effects may be minuscule. By studying QTLs in rodents, researchers may help identify genes that should be studied in humans. QTLs have been identified provisionally for alcohol withdrawal, alcohol preference, and alcohol sensitivity; evidence indicates that QTLs may be under common genetic control (Crabbe et al. 1994; also see the article by Grisel and Crabbe, pp. 220–227).

New directions for genetic analysis may be suggested by results of the Collaborative Study on the Genetics of Alcoholism (COGA). This comprehensive program, involving six research centers across the United States, is investigating the genetic contribution to alcoholism vulnerability. Final analysis of COGA data may reveal potential alcoholism-related genes unrelated to any genes previously thought relevant to alcoholism. (See the article on COGA, pp. 228–236.)

Future study of genetic variants also might focus on some of the more specific and directly heritable alcoholism-related traits, such as variants of brain electrical activity (Enoch et al. in press). Ultimately, gene variants may be used as markers of alcoholism vulnerability and as guides to help match patients to appropriate alcoholism therapies (Goldman 1995). ■

ACKNOWLEDGMENT

The author gratefully acknowledges the assistance of Stefano Michelini, M.D., in the preparation of this article.

REFERENCES

- ABBAR, M.; COURTET, P.; AMADEO, S.; CAER, Y.; MALLET, J.; BALDY-MOULINIER, M.; CASTELNAU, D.; AND MALAFOSSE, A. Suicidal behaviors and the tryptophan hydroxylase gene. *Archives of General Psychiatry* 52(10):846–849, 1995.
- ARINAMI, T.; ITOKAWA, M.; KOMIYAMA, T.; MITSUSHIO, H.; MORI, H.; MIFUNE, H.; HAMAGUCHI, H.; AND TORU, M. Association between severity of alcoholism and the A1 allele of the dopamine D2 receptor gene TaqI A RFLP in Japanese. *Biological Psychiatry* 33(2):108–114, 1993.
- BLANCHARD, D.C.; SHEPHERD, J.K.; RODGERS, R.J.; AND BLANCHARD, R.J. Evidence for differential effects of 8-OH-DPAT on male and female rats in the Anxiety/Defense Test Battery. *Psychopharmacology* 106:531–539, 1992.
- BLUM, K.; NOBLE, E.P.; SHERIDAN, P.J.; MONTGOMERY, A.; RITCHIE, T.; JAGADEESWARAN, P.; NOGAMI, H.; BRIGGS, A.H.; AND COHN, J.B. Allelic association of human dopamine D₂ receptor gene in alcoholism. *Journal of the American Medical Association* 263(15): 2055–2060, 1990.
- BLUM, K.; NOBLE, E.P.; SHERIDAN, P.J.; FINLEY, O.; MONTGOMERY, A.; RITCHIE, T.; OZKARAGOZ, T.; FITCH, R.J.; SADLACK, F.; SHEFFIELD, D.; DAHLMANN, T.; HALBARDIER, S.; AND NOGAMI, H. Association of the A1 allele of the D₂ dopamine receptor gene. *Alcohol* 8:409–416, 1991.
- BLUM, K.; NOBLE, E.P.; SHERIDAN, P.J.; MONTGOMERY, A.; RITCHIE, T.; OZKARAGOZ, T.; FITCH, R.J.; FINLEY, O.; AND SADLACK, F. Genetic predisposition in alcoholism: Association of the D₂ dopamine receptor TaqI B1 RFLP with severe alcoholics. *Alcohol: International Biomedical Journal* 10:59–67, 1993.
- BOHMAN, M. Some genetic aspects of alcoholism and criminality: A population of adoptees. *Archives of General Psychiatry* 35:269–276, 1978.
- BRUNNER, H.G.; NELEN, M.; BREAKFIELD, X.O.; ROPERS, H.H.; AND VAN OOST, B.A. Abnormal behavior associated with a point mutation in the structural gene for monoamine oxidase A. *Science* 262:578–580, 1993.
- CLONINGER, C.R.; BOHMAN, M.; SIGVARDSSON, S.; AND VON KNORRING, A.L. Psychopathology in adopted-out children of alcoholics: The Stockholm adoption study. In: Galanter, M., ed. *Recent Developments in Alcoholism*. Vol. 3. New York: Plenum Press, 1985. pp. 37–51.
- COMINGS, D.E.; COMINGS, B.G.; MUHLEMAN, D.; DIETZ, G.; SHAHBAHAMI, B.; TAST, D.; KNELL, E.; KOCIS, P.; BAUMGARTEN, R.; KOVACS, B.; LEVY, D.L.; SMITH, M.; BORISON, R.L.; EVANS, D.D.; KLEIN, D.N.; MACMURRAY, J.; TOSK, J.M.; SVERD, J.; GYSIN, R.; AND FLANAGAN, S.D. The dopamine D2 receptor locus as a modifying gene in neuropsychiatric disorders. *Journal of the American Medical Association* 266(13):1793–1800, 1991.

- COOK, B.L.; WANG, Z.W.; CROWE, R.R.; HAUSER, R.; AND FREIMER, M. Alcoholism and the D₂ receptor gene. *Alcoholism: Clinical and Experimental Research* 16(4):806–809, 1992.
- CRABBE, J.C.; BELKNAP, J.K.; AND BUCK, K.J. Genetic animal models of alcohol and drug abuse. *Science* 264:1715–1723, 1994.
- DEVOR, E.J. Why there is no gene for alcoholism. *Behavior Genetics* 23(2):145–151, 1993.
- DEVOR, E.J.; CLONINGER, C.R.; KWAN, S.W.; AND ABELL, C.W. A genetic familial study of monoamine oxidase B activity and concentration in alcoholics. *Alcoholism: Clinical and Experimental Research* 17(2):263–267, 1993.
- DE WAELE, J.P.; PAPACHRISTOU, D.N.; AND GIANOULAKIS, C. The alcohol-preferring C57BL/6 mice present an enhanced sensitivity of the hypothalamic β -endorphin system to ethanol than the alcohol-avoiding DBA/2 mice. *Journal of Pharmacology and Experimental Therapeutics* 261(2):788–794, 1992.
- DI CHIARA, G. The role of dopamine in drug abuse viewed from the perspective of its role in motivation. *Drug and Alcohol Dependence* 38(2):95–137, 1995.
- ENOCH, M.A.; ROHRBAUGH, J.W.; DAVIS, E.Z.; HARRIS, C.; ELLINGSON, R.J.; ANDREASON, P.; MOORE, V.; VARNER, J.L.; BROWN, G.L.; ECKARDT, M.J.; AND GOLDMAN, D. Genetic epidemiology and relationship to psychopathology of the low voltage and monomorphic alpha variants of the electroencephalogram. *Neuropsychiatric Genetics*, in press.
- FROEHLICH, J.C. Genetic factors in alcohol self-administration. *Journal of Clinical Psychiatry* 56(Suppl. 7):15–23, 1995.
- GEIMAN, P.V.; RAM, A.; GELERNTER, J.; FRIEDMAN, E.; CAO, Q.; PICKAR, D.; BLUM, K.; NOBLE, E.P.; KRANZLER, H.R.; O'MALLEY, S.; HAMER, D.H.; WHITSITT, F.; RAO, P.; DELISI, L.E.; VIRKKUNEN, M.; LINNOILA, M.; GOLDMAN, D.; AND GERSHON, E.S. No structural mutation in the dopamine D₂ receptor gene in alcoholism or schizophrenia: Analysis using denaturing gradient gel electrophoresis. *Journal of the American Medical Association* 271(3):204–208, 1994.
- GELERNTER, J.; GOLDMAN, D.; AND RISCH, N. The A1 allele at the D₂ dopamine receptor gene and alcoholism. *Journal of the American Medical Association* 269(13): 1673–1677, 1993.
- GIANOULAKIS, C.; BELIVEAU, D.; ANGELOGIANNI, P.; MEANY, M.; THAVUNDAYIL, J.; TAWAR, V.; AND DUMAS, M. Different pituitary β -endorphin and adrenal cortisol response to ethanol in individuals with high and low risk for future development of alcoholism. *Life Sciences* 45(12):1097–1109, 1989.
- GOLDMAN, D. Identifying alcoholism vulnerability alleles. *Alcoholism: Clinical and Experimental Research* 19(4):834–831, 1995.
- GOLDMAN, D., AND ENOCH, M.A. Genetic epidemiology of ethanol metabolic enzymes: A role for selection. In: Simopoulos, A.P., and Childs, B., eds. *Genetic Variation and Nutrition*. Basel, Switzerland: Karger, 1990. pp. 143–160.
- GOLDMAN, D.; DEAN, M.; BROWN, G.L.; BOLOS, A.M.; TOKOLA, R.; VIRKKUNEN, M.; AND LINNOILA, M. D₂ dopamine receptor genotype and cerebrospinal fluid homovanillic acid, 5-hydroxyindoleacetic acid and 3-methoxy-4-hydroxyphenylglycol in alcoholics in Finland and the United States. *Acta Psychiatrica Scandinavica* 86(5):351–357, 1992.
- GOLDMAN, D.; BROWN, G.L.; ALBAUGH, B.; ROBIN, R.; GOODSON, S.; TRUNZO, M.; AKHTAR, L.; LUCAS-DERSE, S.; LONG, J.; LINNOILA, M.; AND DEAN, M. DRD2 dopamine receptor genotype, linkage disequilibrium, and alcoholism in American Indians and other populations. *Alcoholism: Clinical and Experimental Research* 17(2):199–204, 1993.
- GRANT, K.A. The role of 5-HT₃ receptors in drug dependence. *Drug and Alcohol Dependence* 38(2): 155–171, 1995.
- HOFFMAN, B.J.; MEZEY, E.; AND BROWNSTEIN, M.J. Cloning of a serotonin transporter affected by antidepressants. *Science* 254:579–580, 1991.
- JOHNSON, B.K., AND COWEN, P.J. Alcohol-induced reinforcement: Dopamine and 5-HT₃ receptor interactions in animals and humans. *Drug Development Research* 30:153–169, 1993.
- LAPPALAINEN, J.; DEAN, M.; CHARBONNEAU, L.; VIRKKUNEN, M.; LINNOILA, M.; AND GOLDMAN, D. Mapping of the serotonin 5-HT_{1D} autoreceptor gene on chromosome 6 and direct analysis of sequence variants. *American Journal of Medical Genetics (Neuropsychiatric Genetics)* 60(2):157–161, 1995.
- LICHTER, J.B.; BARR, C.L.; KENNEDY, J.L.; VAN TOL, H.H.; KIDD, K.K.; AND LIVAK, K.J. A hypervariable segment in the human dopamine receptor D4 (DRD4) gene. *Human Molecular Genetics* 6:767–773, 1993.
- LIEBER, C.S. Alcohol and the liver: 1994 update. *Gastroenterology* 106(4):1085–1105, 1994.
- LITTEN, R.Z., AND ALLEN, J.P. Pharmacotherapies for alcoholism: Promising agents and clinical issues. *Alcoholism: Clinical and Experimental Research* 15(4):620–633, 1991.
- MANSOUR, A.; CHALMERS, D.T.; FOX, C.T.; MEADOR-WOODRUFF, J.H.; AND WATSON, S.J. Biochemical anatomy: Insights into the cell biology and pharmacology of neurotransmitter systems in the brain. In: Schatzberg, A.F., and Nemeroff, C.B., eds. *The American Psychiatric Press Textbook of Psychopharmacology*. Washington, DC: American Psychiatric Press, 1995. pp. 45–64.
- NIELSEN, D.A.; GOLDMAN, D.; VIRKKUNEN, M.; TOKOLA, R.; RAWLINGS, R.; AND LINNOILA, M. Suicidality and 5-hydroxyindoleacetic acid concentration associated with a tryptophan hydroxylase polymorphism. *Archives of General Psychiatry* 51(1):34–38, 1994.
- NOBLE, E.P. The D₂ dopamine receptor gene: A review of association studies in alcoholism. *Behavior Genetics* 23(2):119–129, 1993.
- NOBLE, E.P.; BERMAN, S.M.; OZKARAGOZ, T.Z.; AND RITCHIE, T. Prolonged P300 latency in children with the D2 dopamine receptor allele. *American Journal of Human Genetics* 54:658–668, 1994.
- PARSIAN, A.; TODD, R.D.; DEVOR, E.J.; O'MALLEY, K.L.; SUAREZ, B.K.; REICH, T.; AND CLONINGER, C.R. Alcoholism and alleles of the human D₂ dopamine receptor locus. *Archives of General Psychiatry* 48(7):655–663, 1991.
- PIHL, R.O., AND PETERSON, J.B. Alcohol, serotonin, and aggression. *Alcohol Health & Research World* 17(2): 113–116, 1993.
- PLOMIN, R. The role of inheritance in behavior. *Science* 248:183–188, 1990.
- RIETSCHEL, M.; NOTH, M.M.; LANNFELT, L.; SCHWARTZ, J.C.; LANCZIK, M.; FRITZ, J.; CICHON, S.; FIMMERS, R.; AND KORNER J. A serine to glycine substitution at position 9 in the extracellular N-terminal part of the dopamine D3 receptor protein: No role in the genetic predisposition to bipolar affective disorder. *Psychiatry Research* 46:253–259, 1993.
- SMITH, S.S.; O'HARA, B.F.; PERSICO, A.M.; GORELICK, D.A.; NEWLIN, D.B.; VLAHOV, D.; SOLOMON, L.; PICKENS, R.; AND UHL, G.R. Genetic vulnerability to drug abuse: The D₂ dopamine receptor Taq 1 B1 restriction fragment length polymorphism appears more frequently in polysubstance abusers. *Archives of General Psychiatry* 49(9):723–727, 1992.
- SUMI-ICHINOSE, C., ET AL. Molecular cloning of genomic DNA and chromosomal assignment of the gene for human aromatic L-amino acid decarboxylase, the enzyme for catecholamine and serotonin biosynthesis. *Biochemistry* 31:2229–2238, 1992.
- THOMASSON, H.R.; CRABB, D.W.; EDENBERG, H.J.; AND LI, T.-K. Alcohol and aldehyde dehydrogenase polymorphisms and alcoholism. *Behavior Genetics* 23(2):131–136, 1993.
- TOLLEFSON, G.D. Selective serotonin reuptake inhibitors. In: Schatzberg, A.F., and Nemeroff, C.B., eds. *The American Psychiatric Press Textbook of Psychopharmacology*. Washington, DC: American Psychiatric Press, 1995. pp. 161–182.
- VIRKKUNEN, M., AND LINNOILA, M. Serotonin in personality disorders with habitual violence and impulsivity. In: Hodgkins, S., ed. *Mental Disorders and Crime*. Newbury Park, CA: Sage, 1993. pp. 227–243.
- VIRKKUNEN, M.; RAWLINGS, R.; TOKOLA, R.; POLAND, R.E.; GUIDOTTI, A.; NEMEROFF, C.; BISSETTE, G.; KALOGERAS, K.; KARONEN, S.L.; AND LINNOILA, M. CSF biochemistries, glucose metabolism, and diurnal activity rhythms in alcoholic, violent offenders, fire setters, and healthy volunteers. *Archives of General Psychiatry* 51(1):20–27, 1994a.
- VIRKKUNEN, M.; KALLIO, E.; RAWLINGS, R.; TOKOLA, R.; POLAND, R.E.; GUIDOTTI, A.; NEMEROFF, C.; BISSETTE, G.; KALOGERAS, K.; KARONEN, S.L.; AND LINNOILA, M. Personality profiles and state aggressiveness in Finnish alcoholic, violent offenders, fire setters, and healthy volunteers. *Archives of General Psychiatry* 51(1):28–33, 1994b.
- VOLPICELLI, J.R.; ALTERMAN, A.I.; HAYASHIDA, M.; AND O'BRIEN, C.P. Naltrexone in the treatment of alcohol dependence. *Archives of General Psychiatry* 49:867–880, 1992.