A Cautionary Genetic Tale: The Sobering Story of D_2

Once burned, twice shy. It can be just as true of a research community as it is of folks in the lay world. Take the case of a putative "alcoholism gene" identified 4 years ago, to much fanfare, by psychiatrist Ernest P. Noble of the University of California, Los Angeles, School of Medicine and pharmacologist Kenneth Blum of the University of Texas Health Science Center in San Antonio. Subsequent attempts to replicate the finding have been largely unsuccessful, and even those whose research appears to confirm it can't come up with a mechanism for the gene's presumed effects. In the eyes of many addiction researchers—along with most human geneticists—the difficulties Blum and Noble's claim has encountered carry a sobering lesson: It's best to be very cautious about publishing findings of new "behavioral genes." In spite of these difficulties, the enthusiasm of Blum and Noble for their find remains undiminished. In fact, they argue that the gene they've targeted is more significant than a mere alcoholism gene—it's a "reward gene" that plays a part in a wide range of compulsive disorders.

The confusion over their finding doesn't mean alcoholism doesn't have a genetic component: Twin, family, and adoption studies have demonstrated that people can inherit a vulnerability to strong drink. But whether it's a specific vulnerability to alcohol or a more general addictive proclivity has not been established, and no one had a serious candidate gene until Blum and Noble reported that one type of receptor for the neurotransmitter dopamine is implicated in severe alcoholism.

Dopamine is the chief neurotransmitter in the brain's "pleasure center," and it has figured prominently in chemical theories of addiction. Blum and Noble examined DNA samples from the brains of 35 deceased alcoholics and found that one variant of the gene for the D_2 receptor—the A1 allele—was present in 69% of the alcoholics but only 20% of an equal number of controls.

It didn't take long for that solid-seeming finding to begin changing its phase. Six months after Blum and Noble's paper was published in the *Journal of the American Medical Association* (*JAMA*), a team at the National Institute on Alcohol Abuse and Alcoholism (NIAAA) announced that it could find no significant difference between alcoholics and nonalcoholics in the frequency of the suspect allele.

Shortly after that finding was also published in *JAMA*, the same journal presented two papers with opposite conclusions in the same issue. One, from a Yale University group headed by psychiatrist Joel Gelernter, came down on the NIAAA's side—saying there was little reason to accept Blum and Noble's conclusion. The other, from medical geneticist David Comings of the City of Hope Medical Center in Duarte, California, supported Blum and Noble. It found that the A1 allele occurred more frequently not only in alcoholics but in people with other disorders involving abnormalities in dopamine transmission—including Tourette's syndrome, attention deficit–hyperactivity disorder, and autism.

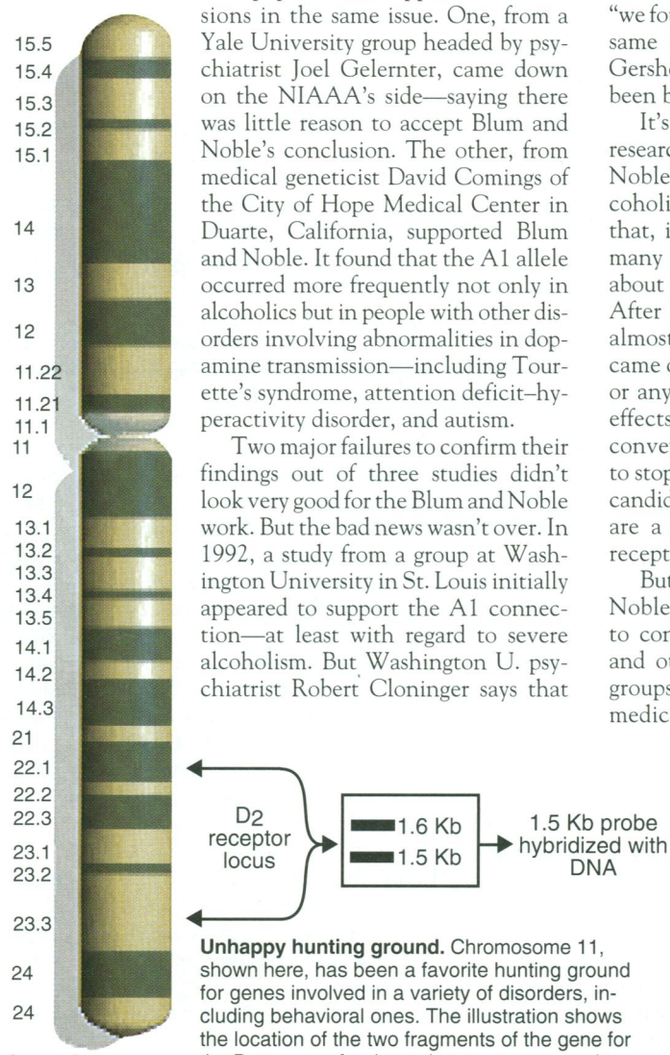
Two major failures to confirm their findings out of three studies didn't look very good for the Blum and Noble work. But the bad news wasn't over. In 1992, a study from a group at Washington University in St. Louis initially appeared to support the A1 connection—at least with regard to severe alcoholism. But Washington U. psychiatrist Robert Cloninger says that when the group expanded its sample, it found, to his "chagrin," that the association between the D_2 receptor and alcoholism faded out. Cloninger published these results early this year.

Most recently, a team at the National Institute of Mental Health (NIMH) hammered the hypothesis with another negative study—this one looking at the D_2 dopamine receptor gene itself rather than at DNA markers. Psychiatric geneticist Elliot Gershon and colleagues did a study of alcoholics and schizophrenics (whose disorder also involves dopamine transmission) in which they used DNA from the alcoholics sampled in previous studies—including the original Blum and Noble work. This time, says Gershon, "we examined the gene instead of the marker," analyzing the complete coding sequence for the D_2 dopamine receptor gene. "We found several coding variants," says Gershon, but "we found the frequency was pretty much the same in the subjects and the controls." Gershon's conclusion: Blum and Noble have been building a "castle in the air."

It's not only those in the field of addiction research who have become cool to Blum and Noble's specific genetic explanation of alcoholism. David Goldman of NIAAA says that, in the larger world, "there aren't too many geneticists who would be sanguine about the authenticity of this association." After all, says Gelernter of Yale, "it's now almost 4 years since [the original] paper came out, and we still don't have a mutation or anything that could directly explain the effects that this A1 allele is supposed to convey." These skeptics argue that it's time to stop focusing on D_2 and move on to other candidate alcoholism genes, of which there are a number, including other dopamine receptor genes.

But Blum and Noble aren't moving on. Noble argues that other studies have failed to confirm their results because alcoholics and other addicts were present in control groups, and that alcoholics with severe medical problems (those most likely to carry the A1 variant, he says), were weeded out of experimental groups. Even more important, he argues, the gene in question is not alcohol-specific but a "reward gene" that leads to reinforcement for a wide range of compulsive behaviors. As a result, he claims, the background level of the allele might be very high in families of alcoholics—thus obscuring the association with alcoholism—if other family members are smokers, overeaters, or other sufferers from what Blum calls "compulsive disease."

Indeed, neurologist George Uhl of the National Institute on Drug Abuse, the main D_2 standard bearer



Unhappy hunting ground. Chromosome 11, shown here, has been a favorite hunting ground for genes involved in a variety of disorders, including behavioral ones. The illustration shows the location of the two fragments of the gene for the D_2 receptor for dopamine, a neurotransmitter. Ernest Noble and Kenneth Blum used DNA hybridization with subjects' DNA to find out whether they carried the A1 allele of that gene. Blum and Noble reported that the A1 allele was linked to severe alcoholism, but several other groups have failed to replicate the finding.

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among government scientists, says the evidence is much stronger for drugs other than alcohol. Last December, Blum and Noble announced that 51% of a group of cocaine addicts possessed the A1 allele—compared with 16% of the controls. Uhl says that among 504 drug abusers covered by four studies, 44% have the allele, compared with 28% of the controls. "The odds that this is a chance finding are getting lower and lower," he says. Goldman of NIMH counters that there are more negative findings around than some realize, but that "as interest has begun to wane somewhat, people who have negative data have lost interest in going through the battle to publish it." Gelernter, for one, says he has unpublished negative findings on a group of cocaine addicts.

Although there's still a group of believers, many regard the D_2 story as troubling. Neuroscientist Henri Begleiter of the State University of New York's Health Science Center at Brooklyn, head of a massive, multicenter alcohol-gene–seeking study, finds it disturbing that Blum and Noble continue to press what Begleiter thinks is a flimsy case. "You'd think they'd be sufficiently concerned to call a meeting of major geneticists and sort this out," he says. Until the ultimate truth about D_2 emerges, the entire episode is making the researchers in Begleiter's own study, now in its fifth year, even more cautious than usual. "Because of the D_2 business," he says, "we are going to make triple sure that something we report is in fact real." And that cautious outlook seems to hold for the field in general.

–Constance Holden

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