



Genes Harbor Clues to Addiction, Recovery

Tracy Hampton, PhD

CHICAGO—Kicking an alcohol or nicotine habit is rarely easy. But scientists analyzing the effects of various genes in addiction and recovery are finding that some individuals may have genetic variants that make it particularly difficult to overcome these dependencies.

New findings presented at the American Psychological Society's annual convention in May implicate genetic variants that affect cell surface receptors and a neurotransmitter involved in the brain's reward system. The hope is that such findings will one day enable scientists to develop new and better ways to help patients with alcohol or smoking problems.

ALCOHOL AND THE OPIOID RECEPTOR

One culprit that may play a role in how well individuals fare in alcohol rehabilitation is the μ -opioid receptor. The presence of alcohol increases brain β -endorphin levels, which trigger neuronal μ -opioid receptors to generate a reward sensation.

The μ -opioid receptor antagonist naltrexone has been shown to limit alcohol intake in animal and human studies. As a result, the Food and Drug Administration (FDA) approved the drug a decade ago for the treatment of alcohol dependence when administered in addition to sobriety counseling. But up to 40% of individuals who are adherent to treatment fail naltrexone therapy, said Wade Berrettini, MD, PhD, of the University of Pennsylvania, in Philadelphia.

"Studies all suggest that there's a great deal of variation in naltrexone response to alcohol dependence, and we don't understand the source of that variation," he added.

Berrettini and colleagues may be on to something, though. They are studying a variant in the μ -opioid receptor gene—a single-nucleotide polymorphism (SNP) known as A118G. (SNPs

are genetic variants, or alleles, involving only a single changed nucleotide. Some result in changes to the protein product encoded by the gene; others do not.) Some individuals have a sequence at the A118G SNP that encodes the amino acid asparagine (due to an adenine nucleotide) while others have a sequence that encodes aspartic acid (due to a guanine nucleotide). Receptors with the guanine allele have a 3-fold increased affinity for β -endorphin.



Scientists are identifying genetic variants that may make it difficult for some individuals to overcome alcohol and nicotine dependencies.

Berrettini's group conducted a post hoc analysis of DNA samples from patients in three double-blind placebo-controlled naltrexone trials. (Two studies incorporated counseling for all groups, and one study randomized all patients to counseling or simple medication management by a physician.) A significantly greater proportion of individuals with the adenine allele (47.9% of 48 individuals) relapsed to heavy drinking compared with those with the guanine allele (26.1% of 23 individuals). In patients receiving placebo, there was no difference in

relapse rates between the two genotypes (*Neuropsychopharmacology*. 2003;28:1546-1552).

"If this result is confirmable, we have a simple genetic test which gives rise to an 85% chance that an individual's going to go through naltrexone coupled with sobriety counseling without a relapse to heavy drinking," said Berrettini.

According to Berrettini, preliminary discussions with the FDA have indicated that the agency would be willing to provide a genotype-specific indication for naltrexone if a randomized study generates similar results. Plans for such a trial are under way, said Berrettini.

TAILORING NICOTINE THERAPIES

As with treatment for alcohol addiction, the success rate of nicotine replacement therapy for smoking is variable. In addition, there are a number of products, including transdermal nicotine patches and nicotine sprays, which have different pharmacological properties. "We may be able to use information about genetic variance that will help us choose the best type of nicotine replacement therapy, the best dose, and the best duration of treatment for individual smokers," said Caryn Lerman, PhD, of the University of Pennsylvania.

Lerman is looking at the same SNP in the μ -opioid receptor gene that Berrettini is studying because nicotine, like alcohol, increases the release of β -endorphin. In 320 smokers of European ancestry, the 82 smokers carrying the guanine variant were significantly more likely than the 238 smokers with the adenine variant to be abstinent at the end of 12-week treatment. The genotype effect on treatment was particularly pronounced with the nicotine patch, which provides a more gradual and stable delivery of nicotine compared with the more potent, yet intermittent nicotine spray (*Pharmacogenomics J*. 2004;4:184-192).



Lerman and colleagues are also studying variants in genes involved in the dopamine pathway with respect to nicotine dependence. Dopamine is associated with the brain's reward system, and scientists have long known that nicotine stimulates the release of dopamine in the brain. The D2-dopamine-receptor gene has a SNP in its promoter region (the part of a gene involved in turning the gene on or off). Lerman and colleagues are investigating whether individuals with cytosine inserted into this promoter region may have decreased numbers of dopamine receptors compared with those without cytosine. The effect of a decreased number of dopamine receptors would be to induce craving and encourage the individual to use nicotine to boost dopamine levels.

"We hypothesized that [individuals] who had the insertion cytosine allele might be at higher risk for relapse because they may be more prone to use nicotine to increase levels of dopamine," said Lerman. Her preliminary results showed that individuals with the insertion cytosine allele had lower overall abstinence rates at the end of nicotine-replacement therapy—either patch or spray—than those without the insertion.

Lerman is also looking at a variant in the catechol-O-methyltransferase gene, which is involved in dopamine metabolism. Higher levels of the gene's encoded enzyme result in decreased dopamine levels. Early results indicated that individuals with the low-activity allele showed no difference in abstinence rates with the two treatments, but

individuals with the high-activity allele were more successful at obtaining abstinence with the patch compared with the spray.

Despite the intriguing results emerging from these pharmacogenetic studies on alcohol and nicotine dependence, more detailed genetic analyses are needed, said Raymond Niaura, PhD, of Brown Medical School, Providence, RI, who gave an overview following the presentations.

"I think there's a real need to drill down, or perhaps more accurately to drill up, from the genome to fully understand addiction," said Niaura. "Genome-wide studies implicate multiple biological pathways [as being involved in addiction], some of which are really not so obvious at all," he added. □

FDA Warns Against Breast Milk Drug

Tracy Hampton, PhD

THE FOOD AND DRUG ADMINISTRATION (FDA) is cautioning breastfeeding women not to use an unapproved drug, domperidone, which may increase the secretion of prolactin and therefore increase milk production. Several published reports and case studies have linked domperidone to cardiac arrhythmias, cardiac arrest, and sudden death in patients receiving an intravenous form of the drug.

More than 2000 reports of adverse effects from 33 countries have been related to domperidone, and the drug has been withdrawn from marketing in a number of countries. Several nations, including Canada, have approved oral domperidone for gastric disorders, as it increases contractions of the stomach and bowel.

But domperidone is not approved in any country for enhancing breast milk production. It is not known if domperidone causes adverse effects in new-

borns, and drug labels on the oral form of the drug note that it is excreted in the milk of lactating women and caution women taking domperidone to avoid breastfeeding.

The FDA alert was issued following the discovery that some women who breastfeed and/or pump breast milk are purchasing the drug from US pharmacies that prepare it from bulk ingredients or from foreign sources. The agency issued six warning letters to pharmacies and firms that supply domperidone, requiring responses that delineate specific steps that will be taken to correct the violations and prevent them from recurring. Further violations may result in seizure and injunction.

The letters issued by the FDA stated that all drug products containing domperidone violate the Federal Food, Drug, and Cosmetic Act because they are unapproved new drugs and mislabeled. In addition, importing domperidone-containing products or distribut-

ing them within the United States violates the law. The agency sent out an Import Alert urging FDA field personnel to be on the lookout for attempts to import this drug into the United States.

A number of Internet sites offer resources for ordering domperidone to breastfeeding women, and many of them downplay the potential health risks of the drug to women and their infants. Although these sites caution that domperidone should be taken only after all other factors that may result in insufficient milk supply have been addressed, the FDA recommends that breastfeeding women not use the drug under any circumstances.

"The FDA recognizes the immense health benefits that breast milk provides for a nursing infant and is taking these actions . . . not to discourage women from breastfeeding but rather to warn them not to use this particular drug while they are breastfeeding," an FDA statement said. □