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Scientists find gene linked to alcoholism

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Researchers from the University of North Carolina at Chapel Hill School of Medicine have discovered a gene variant that may protect against alcoholism.

The variant, in a gene called CYP2E1, is associated with a person's response to alcohol. For the ten to twenty percent of people that possess this variant, those first few drinks leave them feeling more inebriated than the rest of the human population, who harbor a different version of the gene.

Previous studies had shown that people who react strongly to alcohol were less likely to become alcoholics later in life, but the genetic basis of this finding was not clear. Now the discovery of CYP2E1's role hints at a new mechanism of how people perceive alcohol, and further, how alcohol affects the brain.

"We have found a gene that protects against alcoholism, and on top of that, has a very strong effect," said senior study author Kirk Wilhelmsen, M.D., Ph.D., professor of genetics at UNC. "But alcoholism is a very complex disease, and there are lots of complicated reasons why people drink. This may be just one of the reasons."

The study appears in the October 19 on-line (Early View) edition of *Alcoholism: Clinical and Experimental Research* (ACER). It will appear in print in the January 2011 issue of the journal.

The research takes a specific phenotype – the way people feel after

consuming alcohol – and uses it to dissect why some people develop alcoholism and some do not.

In order to tease apart the genetics of alcoholism, Wilhelmsen and his collaborators gathered hundreds of pairs of siblings, all college-age, and all with at least one parent who was an alcoholic. First, the participants were given a mixture of grain alcohol and soda that was equivalent to about three drinks. Then they were asked at regular intervals to answer a number of questions describing how the alcohol made them feel: I feel drunk, I don't feel drunk; I feel sleepy, I don't feel sleepy.

The researchers then conducted time-honored genetic analyses called linkage and association to hone in on the gene region that appeared to influence how the students perceived alcohol.

"So it would be like if you were trying to figure out where someone is in the United States, linkage would get you to the right state, and association would get you to the right neighborhood," said Wilhelmsen.

The neighborhood Wilhelmsen located is home to the CYP2E1 gene. This gene has long held the interest of researchers interested in alcoholism, because it encodes an enzyme that can metabolize alcohol. Most of the alcohol in the body actually gets metabolized by another enzyme, alcohol dehydrogenase, which works in the liver. But CYP2E1 doesn't work in the liver; it works in the brain. And it works differently than other enzymes, generating tiny molecules called free radicals, which can be reactive and rather nasty to sensitive structures like brain cells.

"It turns out that a specific version or allele of CYP2E1 makes people more sensitive to alcohol, and we are now exploring whether it is because it generates more of these free radicals," said Wilhelmsen. "This finding is interesting because it hints at a totally new mechanism of how we perceive alcohol when we drink. The conventional model basically

says that alcohol affects how neurotransmitters, the molecules that communicate between neurons, do their job. But our findings suggest it is even more complex than that."

In the future, drugs that induce CYP2E1 could be used to make people more sensitive to alcohol before they've taken their first drink, or even to help sober them up when they've had one too many. But Wilhelmsen thinks the most exciting aspect of his finding is that it could change the focus of how research into the underpinnings of alcoholism is conducted.

Provided by University of North Carolina School of Medicine