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Gene variation makes alcoholism less likely in some survivors of sexual abuse

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Exposure to severe stress early in life increases the risk of alcohol and drug addiction. Yet surprisingly, some adults sexually abused as children — and therefore at high risk for alcohol problems — carry gene variants that protect them from heavy drinking and its effects, according to researchers at Washington University School of Medicine in St. Louis.

The researchers, from the university's Midwest Alcoholism Research Center, say the finding could aid the development of therapies for alcohol dependence by offering suggestions for targeted treatments based on genetic traits and history of exposure to severe stressors.

Scientists estimate that about half the risk for alcoholism is encoded in a person's genes. The rest comes from environmental factors, such as age at first drink and exposure to extreme stress. Other research has suggested that when the environmental risk factors occur during key periods of brain development, genes and environment working together can increase the likelihood an individual will become alcohol dependent. Child sexual abuse is one of the environmental stressors that can interact with genes to significantly increase the risk for alcohol problems.

But the researchers report in the January issue of *Addiction Biology* that people with a particular pattern of genetic markers seem to be protected against alcohol problems, even if they were sexually abused as children.

Those who were protected carry a set of genetic variations that scientists call the H2 haplotype. Similar to a blood type, a haplotype is more than

just a single genetic mutation. It is a normally occurring pattern of gene variants that are statistically associated with one another so that when scientists find a few genetic markers, they can successfully predict what other genetic variations will occur within a particular region of DNA.

"We looked at how genes and environment interact," says Elliot C. Nelson, M.D., lead author of the study. "Our analysis included both sexual abuse and information about the DNA region that carries the H2 haplotype. People who carry that genetic pattern were protected against the risks for alcohol consumption and alcohol dependence typically associated with sexual abuse."

Other sexual abuse victims in the study had the alternate genetic pattern known as the H1 haplotype. Those individuals had three times the risk of heavy drinking and alcohol dependence as those who had not been sexually abused.

"They drank much more alcohol and had a significantly greater risk for problems," says Nelson, an associate professor of psychiatry. "But abuse victims with the H2 haplotype seemed to be completely protected against those risks."

Nelson's team studied data from more than 1,100 people in 476 Australian families who participated in the Nicotine Addiction Genetics project. Originally, that study was set up to learn about nicotine addiction, but investigators also looked at related problems, including how much alcohol people drank and whether they met the diagnostic criteria for alcohol dependence.

Study subjects also were asked about sexual abuse in childhood. A total of 121 women and 35 men reported a history of sexual abuse beginning at around age 11. Nelson's group also had access to DNA samples from those evaluated in this study.

By identifying a handful of specific sites in the genome, it's possible to classify a person as having either the H1 or the H2 haplotype. One of the genes in the DNA region included in H1 and H2 is called corticotropin releasing hormone receptor type 1 (CRHR1). Nelson's group is focusing on that gene, which research in animals has implicated in risk for alcohol dependence.

Many past studies have focused on genes related to alcohol metabolism, but CRHR1 is not a metabolism gene. Nelson says it appears from animal studies, however, that the gene may be involved in risks associated with the effects of environmental stress. In the case of humans, he suspects variants of the gene may play a role in protecting against stresses caused by child sexual abuse.

"There are many different ways an individual can become alcoholic, some involving heavy genetic risks, some involving specific environmental factors, such as exposure to peers who drink heavily," Nelson says. "This particular pathway involving CRHR1 is interesting because it seems to play an extremely important role in animal models of alcohol consumption and dependence."

He says better understanding of how the gene works may help scientists understand the process by which people become alcoholics. As they attempt to clarify the possible role of the CRHR1 gene in protecting sexual abuse survivors from alcohol dependence, Nelson says it may be interesting to look at other severe environmental stressors that trigger alcohol use to see whether people with the H2 variation also are protected from those forms of risk.

In addition, he says drugs have been developed that block CRHR1 receptors. If it turns out that humans are responding to the same stressors and reacting via the same genetic pathway that animals do, Nelson says some of those drugs may be able to help people who are alcoholic using

the same pathway that protects people with the H2 haplotype.

A panel of leading alcoholism researchers will discuss important findings from translational and other genetic research and their implications for treatment at Washington University School of Medicine during the 10th annual Guze Symposium on Alcoholism. The topic of the Feb. 18 meeting is Disentangling the Genetics of Alcoholism: Understanding Pathophysiology and Improving Treatment.

More information: Nelson EC, Agrawal A, Pergadia ML, Wang JC, Whitfield JB, Saccone FS, Kern J, Grant JD, Schrage AJ, Rice JP, Montgomery GW, Heath AC, Goate AM, Martin NG, Madden PAF. H2 haplotype at chromosome 17q21.31 protects against childhood sexual abuse-associated risk for alcohol consumption and dependence. Addiction Biology, vol. 15 (1); pp. 1-11, Jan. 2010. doi:10.1111/j.1369-1600.2009.00181.x

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