The aldehyde dehydrogenase-2 polymorphism affects alcohol dependence differently by gender

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Researchers know that gender differences exist in the prevalence, characteristics, and course of alcohol dependence (AD). Polymorphisms of alcohol dehydrogenase-1B (ADH1B) and aldehyde dehydrogenase-2 (ALDH2) are strong genetic determinants of AD. A new study of gender differences in the effects of these polymorphisms on the development of AD has found that inactive ALDH2 can accelerate the development of AD in women.

Results will be published in the November 2011 issue of *Alcoholism: Clinical & Experimental Research* and are currently available at Early View.

"Alcohol dependence (AD) is much more common among males than females," said Mitsuru Kimura, chief scientist in the department of psychiatry at the Kurihama Alcoholism Center in Japan as well as corresponding author for the study. "However, female alcoholics are more likely to have co-existing psychiatric disorders than male patients."

Victor Hesselbrock, professor of psychiatry at the University of Connecticut School of Medicine, concurred. "Females with AD typically have a greater prevalence of affective problems such as depression and anxiety than males, while males with AD typically display more associated behavioral problems – including antisocial personality disorder – and have higher rates of co-morbid drug problems," he said.

"In general, females have a later onset of AD but typically come to treatment earlier than males. More recently, however, trends indicate that females born in more recent birth cohorts – after 1970 or so – are looking more like males in their clinical picture, for example, age of onset of drinking behaviors, including onset of dependence, and associated problems, including drug problems. Usually gender differences have been attributed to differences in size, such as body mass, body water and/or exposure to alcohol. None of these previous studies ever considered any genotypic information, such as ADH1B or ALDH, as possible explanations for gender differences."

"The two polymorphisms we examined are the most evident genetic determinants of the disease," said Kimura. "ADH1B and ALDH2 eliminate most of the alcohol taken into the body. A lack of ALDH2 activity causes a 'flushing response' which includes flushing, nausea, and a headache after drinking, so it tends to greatly suppress people's drinking."

"ADH is important for the initial metabolism of ethanol into acetaldehyde, while ALDH is important for metabolizing acetaldehyde, the first by-product of ethanol metabolism, into acetate and water," said Hesselbrock. "A variant of the ALDH gene, ALDH2*2 … is relatively common in select Asian populations, approaching 50 percent, but is absent in the homozygous form in Caucasian populations. The allele frequency of these two polymorphisms does not vary by gender."

Kimura and his colleagues examined 615 individuals (415 men, 200 women) hospitalized for AD in the Kurihama Alcoholism Center. Clinical information and background data were gleaned from chart reviews, and ALDH2 and ADH1B genotyping were performed.

Results indicated that ALDH2 polymorphisms appear to have contrasting effects on the development of AD among men and women.

While females typically cannot drink as much as males because of their smaller body size, current findings suggest that differences in alcohol metabolism due to genetic factors may also help explain morbidity differences both between and within genders apart from their different levels of drinking.

"Usually the painful experience of flushing response caused by inactive ALDH2 suppresses alcohol drinking," said Kimura, "but our findings suggest that women who have co-existing psychiatric disorders might be motivated to drink heavily in order to cope with the symptoms of their psychiatric disorders." This suggests a "gene-gender interaction" in the development of AD, meaning that the same genetic factor has a different effect on the different genders.

"In addition, our results might suggest female AD has two types: one is characterized by early-onset and a high prevalence of psychiatric comorbidity; the other by late-onset and a relatively low prevalence of psychiatric comorbidity," said Kimura. "The early-onset subtype likely has a primary psychiatric disorder, and the psychiatric comorbidity likely caused secondary alcohol-related problems. In this subtype, alcohol consumption is scarcely suppressed by the flushing response induced by inactive ALDH2. On the other hand, the middle- or late-onset subtype likely has AD as primary with a low prevalence of psychiatric comorbidity. This subtype commonly increases alcohol consumption to reduce stress or to enjoy social activities, and results in AD. This subtype is more similar to the pattern of male AD and is suppressed by inactive ALDH2."

"This study demonstrates that some genotypes may also be useful phenotypes," said Hesselbrock, "helping us to better describe and understand variations in the expression of alcoholism between patients and possibly provide clues to the clinical course. Furthermore, these findings, if replicated, could be quite useful for the clinician. Currently

clinicians have no objective biological variables available for use in helping them diagnose and develop treatment plans for patients. Additional studies may identify differences in the course of alcoholism or differences in treatment response to certain medications based upon these genotypes."

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