

ALCOHOL DEHYDROGENASE GENOTYPE, MATERNAL ALCOHOL USE, AND INFANT OUTCOME - WHERE ARE WE NOW?

Marjie L. Hard, Graduate Student, School of Pharmaceutical Sciences, University of Toronto

A CRITICAL REVIEW of “Alcohol dehydrogenase 2 genotypes, maternal alcohol use, and infant outcome.” *Joan M. Stoler, MD, Louise M. Ryan, PhD. and Lewis B. Holmes, MD J Pediatr 2002; 141: 780-785*

This study is the most recent of several¹⁻⁴ that have attempted to determine whether polymorphisms in ethanol metabolizing enzymes influence the risk for Fetal Alcohol Spectrum Disorder (FASD). In this study, alcohol using and non-alcohol using pregnant women were recruited from a substance abuse clinic at an inner-city hospital and a general obstetric clinic. Patients were asked about their alcohol use each time they returned to the obstetrics clinic and were categorized according to their frequency of consumption. A physician who was blind to the exposure status examined the infants after birth and diagnosed affected infants using growth parameters and facial features characteristic of alcohol-affected individuals. DNA was extracted from maternal and fetal blood samples for determining ADH2 genotypes.

ADH2 genotypes are reported for 404 women and 139 of their infants. The frequency of the ADH2-3 allele, a high-activity ADH that can potentially produce higher levels of acetaldehyde, was significantly higher in African American women (46%) than in Caucasian women (2%). It was found that women with the ADH2-1/3 genotype tended to drink more than those with the ADH2-1/1 genotype but the difference was not significant.

Infant outcome correlated with genotype and the results suggested that women with the ADH2-1/3 genotype are at greater risk for having an affected infant. The frequency of the ADH2-3 allele was higher in the mothers of affected infants than in those with unaffected infants for both

African American (64% vs. 43%) and Caucasian (8% vs. 1%) races. Accordingly, the ADH2-1 allele was more frequent in the mothers of unaffected than those with affected infants. The same trends were observed in infant genotypes with the ADH2-1/3 genotype being more common in affected than in unaffected infants for both the African American (60% vs. 29%) and Caucasian (20% vs. 5%) offspring. The logistic regression analysis of the entire sample revealed a significant association between infant outcome and the ADH2-1/3 genotype in addition to other confounding variables including smoking, very high alcohol consumption, and maternal weight gain.

The final conclusion of this study was that the ADH2-1/3 genotype may put the fetus at risk for having alcohol-associated abnormalities, which may be a result of higher alcohol consumption that is associated with this genotype. These findings are in agreement with one previous study¹ but contradict others²⁻⁴. Where Stoler et al. attribute the increased risk associated with the ADH2-3 allele to drinking behavior, Sokol et al.¹ accredited it to potentially higher levels of acetaldehyde in fetuses with the ADH2-3 allele. Conversely, other studies have found that the offspring of drinking mothers with the ADH2-3 allele had better neurobehavioral and growth outcomes than those mothers without it, suggesting a protective effect of ADH2-3^{2,3}. It is speculated that the mechanism of this protective effect is the more efficient elimination of ethanol at high blood alcohol concentrations, exposing the fetus to less alcohol⁵. Unlike Stoler et al., Jacobson et al.³ reported that women without the ADH2-3 allele tended to drink more, conferring more risk to the fetus. In another study, Viljoen et al.⁴ genotyped FAS infants and their mothers in a mixed ancestry population of the Western Cape Province of South Africa. Contrary to the latter studies, the frequency of the ADH2-3

allele was not significantly different in the FAS children and their mothers in comparison to the control group. However, the FAS children and their mothers had a significantly lower frequency of the ADH2-2 allele when compared to the control group, suggesting that ADH2-2 is protective against FAS or may prevent FAS by lowering the risk for alcoholism^{6,7}.

The lack of consistency among studies may be due to a number of reasons. Firstly, the endpoints used to assess infant outcome vary. Whereas, some studies,^{1,4} including the one by Stoler et al., use the FAS phenotype, others use neurobehavioral measures alone^{2,3}. The age of diagnosis is also important because FASD is most accurately diagnosed in older, school aged, children^{8,9}. Stoler et al. limited their diagnosis to the newborn period. The association between drinking behavior and ADH2 polymorphisms is an important consideration when interpreting such studies. The finding by Stoler et al. that the ADH2-3 allele is associated with higher ingestion of alcohol is not supported by others^{3,10,11}. Finally, the findings obtained from one ethnic population may not be extrapolated to other populations as indicated by the study by Viljoen et al.⁴; the ADH2-3 allele was not an important factor in their population as it may be in the African American population.

For future studies, more uniform approaches should be taken with respect to diagnosing affected infants and in methods of categorizing the amount of alcohol exposure. Until such uniformity is put forth the difficulty involved with combining the results of these types of studies remains. Although no conclusions can be drawn at this point, the suggestion that there is a pharmacogenetic effect involved in putting some ethnic populations at greater risk for having affected infants should be further explored. It has been suggested that African Americans are at a higher risk for FASD but this has been attributed to a low socioeconomic status¹². If the results of this study are confirmed by others, and possessing the ADH2-3 allele does put a women at greater risk for having a child with FASD, a genetic marker could be used for identifying those at the highest risk for having an affected child.

REFERENCES

1. Sokol RJ, Smith M, Ernhart CB, Baumann R, Martier SS, Ager JW, and Morrow-Tlucak M. A genetic basis for alcohol-related birth defects (ARBD)? *Alcohol Clin Exp Res.* 1989;13:343A.
2. McCarver DG, Thomasson HR, Martier SS, Sokol RJ, Li T. Alcohol dehydrogenase-2*3 allele protects against alcohol-related birth defects among African Americans. *J.Pharmacol.Exp.Ther.* 1997;283(3):109 5-101.
3. Jacobson SW, Chiodo L, Jester J, Carr L, Sokol R, Jacobson J, and Li TK. Protective effects of ADH2*3 in African American infants exposed prenatally to alcohol. *Alcohol Clin Exp Res.* 2000;24 (5 Suppl):28A.
4. Viljoen DL, Carr LG, Foroud TM, Brooke L, Ramsay M, Li TK. Alcohol dehydrogenase-2*2 allele is associated with decreased prevalence of fetal alcohol syndrome in the mixed-ancestry population of the Western Cape Province, South Africa. *Alcohol Clin Exp Res* 2001;25(12):1719-22.
5. McCarver DG. ADH2 and CYP2E1 genetic polymorphisms: risk factors for alcohol-related birth defects. *Drug Metab Dispos.* 2001;29(4 Pt 2):562-5.
6. Chen CC, Lu RB, Chen YC, Wang MF, Chang YC, Li TK et al. Interaction between the functional polymorphisms of the alcohol- metabolism genes in protection against alcoholism. *Am.J Hum.Genet.* 1999;65(3):795-807.
7. Borrás E, Coutelle C, Rosell A, Fernandez-Muixi F, Broch M, Crosas B et al. Genetic polymorphism of alcohol dehydrogenase in europeans: the ADH2*2 allele decreases the risk for alcoholism and is associated with ADH3*1. *Hepatology* 2000;31(4):984-9.
8. Little BB, Snell LM, Rosenfeld CR, Gilstrap LC, III, Gant NF. Failure to recognize fetal alcohol syndrome in newborn infants. *Am.J Dis.Child* 1990;144(10):1142-6.
9. Clarren SK, Randels SP, Sanderson M, Fineman RM. Screening for fetal alcohol syndrome in primary schools: a feasibility study. *Teratology* 2001;63(1):3-10
10. Ehlers CL, Gilder DA, Harris L, Carr L. Association of the ADH2*3 allele with a negative family history of alcoholism in African American young adults. *Alcohol Clin.Exp.Res.* 2001;25(12):1773-7.
11. Wall TL, Carr LG, Ehlers CL. Protective association of genetic variation in alcohol dehydrogenase with alcohol dependence in Native

American mission Indians. Am.J.Psychiatry
2003;160(1):41-6.

12. Abel EL. An update on incidence of FAS: FAS is not an equal opportunity birth defect. Neurotoxicol.Teratol. 1995;17(4):437-43.