A Still Illusive Expectation: Prediction of the Risk of Fetal Alcohol Syndrome Based on Maternal Genotype and Alcohol Use in Pregnancy

Arthur Falek, Ph.D.

Over more than a decade several intriguing articles have been published speculating on the potential that in humans, polymorphisms i.e., allelic variations, in the alcohol metabolizing enzyme genes may be genetic markers of risk for fetal alcohol syndrome to the child of a woman who drinks alcohol during pregnancy. These genetic theories have focused on variations in individuals in the amount of alcohol consumed during pregnancy, in the rate of the metabolism of alcohol in the liver to several classes of alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH1). Mitochondrial ALDH2 is located in the cell body outside the nucleus and is responsible for the metabolism of acetaldehyde to acetate. In populations, the frequencies of the different alleles have been found to exist by race for ADH2, ADH3 and ALDH2 and each allelic class has been found to have differing enzymatic activity (Stoler et.al. J. Pediatr. 2002).

The ADH2*3 allele is found almost exclusively in those of African descent with a very low frequency in Caucasians and has been thought to be an important risk factor for FAS in infants of those pregnant women of African descent who drink alcohol during pregnancy. This is supported by the data presented in the above noted Stoler et. al. publication who reported that women with the ADH2-1/3 genotype had significantly higher alcohol use during their pregnancies and a significantly higher chance of having children with growth retardation and/or the facial features of FAS. In an editorial accompanying the Stoler et.al. article Christina Chambers and Kenneth L. Jones, (the latter, the codiscoverer of FAS in the United States) have written a thoughtful paper.
reviewing the limitations and complexities of the predictive findings presented by the four published papers. In contrast to the Stoler et.al. findings, two of three other studies concerned with this issue, found that the presence of a maternal ADH2*3 allele was in fact protective against the adverse effects of alcohol in the children of African-Americans rather than causative of the syndrome under investigation. McCarver et.al. J. Pharmacol.Exper.Ther.1997 found that based on the Balej Scales of Infant Development Index at 12 months of age and newborn growth parameters demonstrated a significant decrease in newborn growth and lower developmental scores in children of the drinking mothers who lacked an ADH2*3 allele and these findings were confirmed by Jacobson et.al. Alcohol Clin.Exp. Res.2000 who found adverse neurobehavioral effects in 7.5 year old children of alcohol drinking mothers who did not have the ADH2*3 allele and observed normal neurobehavioral results in those who carried this allele. Viljoen et.al. Alcohol Clin.Exp.Res. 2001 conducted his study in a small mixed-ancestry population in South Africa. What he found was that the frequency of the ADH2*3 allele was not significantly different in the FAS children and their mothers in comparison to the control group. On the other hand, the FAS children and their mothers had a significantly lower frequency of the ADH2-2 allele compared to the control group. This suggests that ADH2-2 was either protective against FAS or may have prevented FAS in the study population by lowering the risk for alcoholism in these mothers during their pregnancies.

What is found, therefore is a lack of consistency among these studies as to diagnosis including the age of the child at time of diagnosis, from infancy to 7.5 years of age; the consistent factors basic to the diagnoses of these children; information as to the
amounts of alcohol consumed by these women during their pregnancies; the ADH2 polymorphisms observed in mothers and infants and the birth outcomes as to the fetal alcohol spectrum disorders. Until these issues are resolved, the relationship of the amount of maternal alcohol use with the mother’s specific alcohol dehydrogenase genotype and infant outcome with regard to this specific spectrum of disorders will not be resolved. In addition to the Editorial in the J. Pediatr. 2002 a news report last month by M.L. Hart for the new J.FAS Int. 2003 reviewed these four papers and came to a similar conclusion as the one reported in the J. Pediatr. 2002 Editorial. However, the J. FAS reviewer went on to suggest that if the”ADH2*3 allele does put a woman 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.”

For further information regarding this article please contact the Maternal Substance Abuse and Child Development Project, Emory University School of Medicine, Department of Psychiatry and Behavioral Sciences, Emory West Campus, 1256 Briarcliff Road N.E., Suite 323-West, Atlanta GA, 30306. You can email us at msacd@listserv.cc.emory.edu, visit our website at http://www.emory.edu/MSACD, or phone us at 404-712-9800.

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References:


