

Abstract

Fetal alcohol syndrome (FAS) is a common cause of mental retardation and is attributable to the teratogenic effects of alcohol exposure in utero in individuals with genetic susceptibility. The Coloured communities from the Western and Northern Cape regions have some of the highest recorded incidence rates (~70 affected children per 1000 live births) in the world.

The candidate genes selected for this study belong to the family of alcohol dehydrogenase genes that code for enzymes which metabolise alcohol. The ADH1B and ADH1C genes have previously been examined in the Western Cape Coloured community and the enzyme encoded by the allele ADH1B*2 was significantly associated with protection against the development of FAS. ADH4, a new candidate gene, was selected due to its role in both the alcohol and retinol metabolic pathways.

A case-control genetic association study was performed to examine the potential roles of the ADH1B, ADH1C and ADH4 genes in the etiology of FAS in two Coloured populations from the Northern and Western Cape. Single nucleotide polymorphisms found within the candidate genes were typed by PCR-based methods in samples from the FAS children, their mothers and controls.

Significant associations were observed in the Western Cape cohort but were not replicated in the Northern Cape. Allelic association tests revealed that ADH1B*2 may be a protective marker as it occurred more commonly in the controls than the mothers ($p=0.038$). The alleles of the polymorphic variant, ADH4.8, have been shown to influence the promoter activity of ADH4 (the 'A' allele has been shown to increase the activity of the promoter when compared to the 'C' allele at the same position). The alleles of this polymorphic marker were significantly associated with the risk for FAS. The 'A' allele was shown to occur more commonly in the mothers and FAS-affected children ($p=0.002$ and 0.035 respectively) when compared to the controls, suggesting a role in disease susceptibility while the 'C' allele was shown to occur more commonly in the controls. It

was also observed that ADH1B and ADH4.8 when examined together in a haplotype demonstrated an association with susceptibility to the disease. While the 2-C haplotype (ADH1B-ADH4.8) was shown to be associated with protection against the development of FAS, the 1-A haplotype was associated with increased susceptibility. The results suggest that mothers with the common ADH1B*1 allele and presumably a normal ADH1B function but an increased level of ADH4 (allele 'A') as a result of the promoter mutation, will, when the blood alcohol concentration is high, have an increased risk of having a child with FAS. Conversely when the mothers have a faster alcohol metabolising rate due to the allele ADH1B*2 and normal levels of ADH4 protein (allele 'C'), the circulating alcohol in the blood is removed efficiently resulting in maternal protection against developing the disease.

This study has also highlighted the genetic diversity within individuals of the South African Coloured population. Haplotype analysis and logistic regression revealed that the Western and Northern Cape Coloured communities are genetically different and as a result, the samples could not be pooled for analysis. Although the two groups of controls were genetically diverse, haplotype analysis revealed that the sample of mothers and FAS-affected children were not statistically different between the provinces thus possibly suggesting a similar genetic etiology for the disease. The results from this study suggest that the ADH genes do play a role in the pathogenesis of FAS.