

Full Length Research Paper

Comparative genetics of alcoholism in the Kenyan populations

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Hepatic alcohol dehydrogenase and aldehyde dehydrogenase are major enzymes in the metabolism of exogenous ethanol. These enzymes are polymorphic and are involved in alcohol drinking and risk of alcoholism in some world populations. Three hundred and seventy one samples of hair root lyzates from five Kenyan communities were screened for ADH 2, ADH 3 and ALDH 2 polymorphisms via isoelectric focusing. Additional information on alcohol drinking behaviour, alcohol intake, frequency of alcohol drinking, preference of alcoholic drinks, and alcohol dependence was collected via interview and questionnaire. SAS JPIN statistical program was used to analyze obtained data using chi-square, Anova and t-tests. The results showed that ADH 2*2, ADH 3*1 and ALDH 2*2 alleles do not have protective properties against risk of alcoholism in the selected Kenyan populations. Other factors than ADH and ALDH polymorphisms interfered in the protective mechanism of the latter alleles against excessive alcohol drinking.

Key words: Alcohol, ADH, ALDH, polymorphism, alcohol drinking, alcoholism.

INTRODUCTION

Alcoholism is thought to be a multifactorial disease with complex mode of inheritance in addition to psychological and social factors (WHO, 1993). Many studies of family, adoption and twins in relation to alcoholism have revealed that hereditary factor is an important determinant for developing alcoholism. Genetics and pharmacokinetics of alcohol determine variations of alcohol metabolism among alcohol users and therefore, influence alcohol drinking behaviour and risk of alcoholism. Most ethanol elimination occurs by alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) systems via oxidation of ethanol to acetaldehyde and acetic acid (Crabb, 1995). Both enzymes show functional polymorphism at ADH 2, ADH 3 and ALDH 2 loci and exhibit variation in occurrence in different

populations (Smith 1986; Yoshida et al., 1991; Bosron et al., 1993).

It has been observed that the allele frequencies of ADH 2*2, ADH 3*1 and ALDH 2*2 are significantly decreased in alcoholics in comparison to general population of East Asians (Thomasson et al., 1991; Higuchi et al., 1994; Shen et al., 1997; Chen et al., 1999). It was hypothesized by Thomasson et al. (1991) that sensitivity to alcohol via fast production or slow removal of acetaldehyde determines protective properties of ADH 2*2, ADH 3*1 and ALDH 2*2 alleles among alcohol users. Linkage disequilibrium between ADH 2 and ADH 3 and dominance by the ALDH 2*2 variant are important factors contributing to interactions between genes of the alcohol metabolizing enzymes (Chen et al., 1999).

In this project the hypothesis of protective properties of ADH 2*2, ADH 3*1 and ALDH 2*2 against excessive alcohol drinking and alcoholism were tested in the different Kenyan populations. Other factors than ADH

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and ALDH polymorphisms as sensitivity to alcohol, alcohol intake, mode of alcohol drinking and preference of alcoholic drinks may contribute to biological control of alcohol drinking.

MATERIALS AND METHODS

Samples of hair strands for ADH and ALDH polymorphism analysis were collected in five geographical locations of Kenya from residents of these areas: Kolweny trading center and Siaya (both in Nyanza Province); Longisa (Rift-Valley Province); Limuru (Central Province) and Rugunga (Western Province).

Subjects

All 371 subjects were adult volunteers, females and males, age 18 and above, without serious current disorders, drinkers and nondrinkers. Local medical officers helped in the diagnosis of alcohol dependence and alcoholism using ICD-10 diagnostic criteria (WHO, 1993) in medical examination of participants in the study group. Individuals of the study group were interviewed for alcohol intake, mode of drinking, frequency of alcohol intake, preference of alcoholic drinks, alcohol drinking experience and the age of regular drinking. Informed consent was obtained from all individuals.

Phenotyping of hair strands for ADH/ALDH polymorphism

Samples of hair root lysates were phenotyped for ADH 2, ADH 3 and ALDH 2 isoenzymes via isoelectric focusing in PAAG as described by Kershengolts (1994). The obtained bands of ADH 2 and ADH 3 after isoelectric focusing and specific enzymatic staining were interpreted with the use of the scheme described by Harada et al. (1978a). Heterogeneity of ALDH 2 was observed using the presence/absence (or very low activity) test (Harada et al., 1978b). Genotype and allele frequencies in the groups were calculated by direct counting. Differences in genotype and allele frequencies were tested for significance using the χ^2 -test or Fisher's exact test. Statistical analysis of the data was performed using JMPIN SAS software for Windows.

RESULTS

The Limuru, Siaya, Rugunga and Kolweny populations had the lowest proportion of alcoholics in the study groups in Figure 2). Comparative analysis of ADH and ALDH polymorphism among alcoholics comparison to the Longisa population; $p < 0.0001$, $\chi^2 = 74.840$ (Figure 1). However, the difference in alcohol consumption among alcohol drinkers of the same communities was not statistically significant, $p < 0.3352$, $F = 1.1471$ (and nonalcoholics of the Kenyan populations showed that alcoholics from the Longisa ($p < 0.0003$, $\chi^2 = 21.414$), Kolweny ($p < 0.0171$, $\chi^2 = 8.132$) and Siaya ($p < 0.2349$, $\chi^2 = 2.897$) populations had high proportion of ADH 2*2 allele carriers in comparison to nonalcoholics although the difference did not reached statistical significance level in the Siaya study group. While in the Limuru and the Rugunga populations nonalcoholics had higher proportion

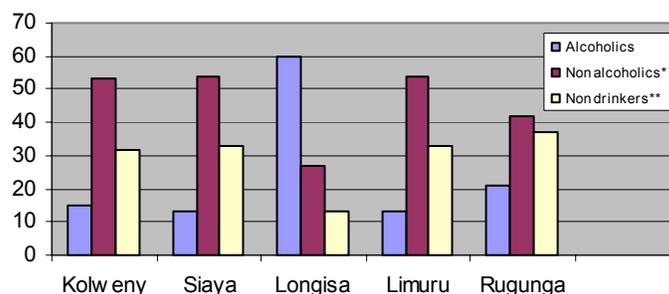


Figure 1. Proportion (%) of alcoholics, nonalcoholics and nondrinkers in the Kenyan populations.

*Nonalcoholics are alcohol drinkers without symptoms of alcohol dependence.

**Nondrinkers are alcohol abstainers.

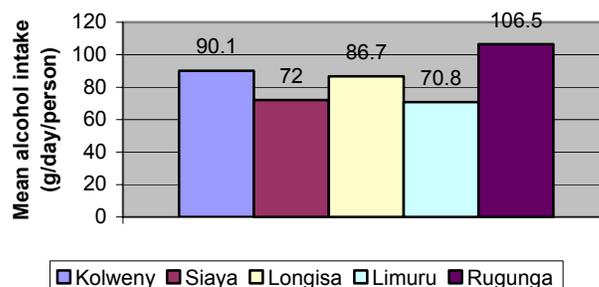


Figure 2. Alcohol intake by drinkers* in the Kenyan populations.

*Drinkers are alcoholics and drinking nonalcoholics.

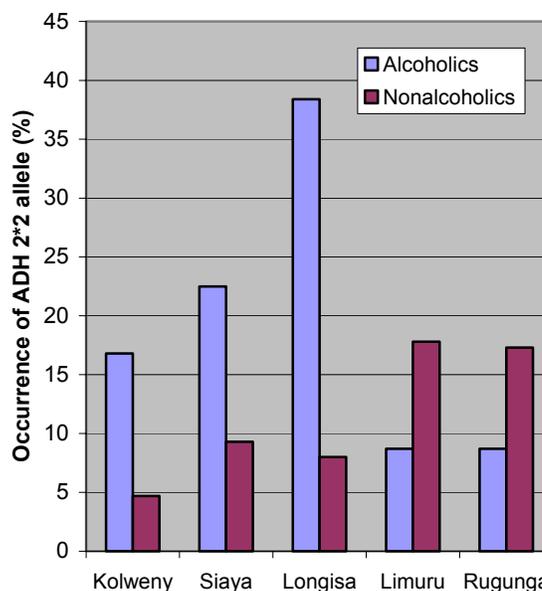


Figure 3. Occurrence of ADH 2*2 alleles among alcoholics and nonalcoholics* in the Kenyan populations.

*Nonalcoholics are alcohol drinkers without symptoms of alcohol dependence.

of ADH 2*2 allele in comparison to alcoholics ($p < 0.0030$, $\chi^2 = 16.042$ and $p < 0.0084$, $\chi^2 = 13.680$, respectively) (Figure 3). At the ADH 3 locus, alcoholics and nonalcoholics from the different Kenyan populations did not differ significantly in allele and genotype polymorphism (Figure 4). At the ALDH 2 locus, alcoholics of the Siaya and the Longisa populations had higher occurrence of ALDH 2*2 allele in comparison to nonalcoholics ($p < 0.0860$, $\chi^2 = 4.907$ and $p < 0.0236$, $\chi^2 = 7.491$ respectively). Alcoholics and nonalcoholics of the Kolweny, Limuru and Rugunga populations did not differ significantly in ALDH 2 polymorphism (Figure 5).

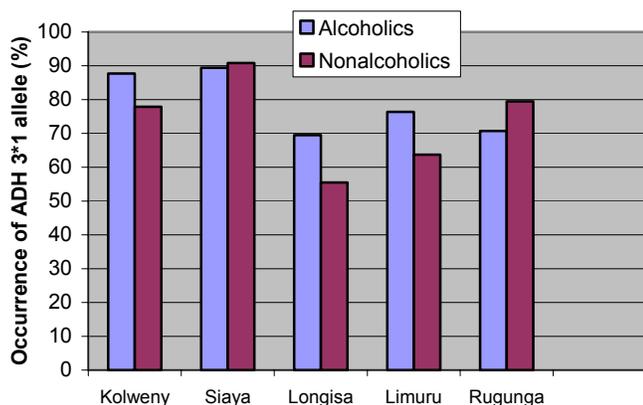


Figure 4. Occurrence of ADH 3*1 allele among alcoholics and nonalcoholics* in the Kenyan populations.

*Nonalcoholics are alcohol drinkers without symptoms of alcohol dependence

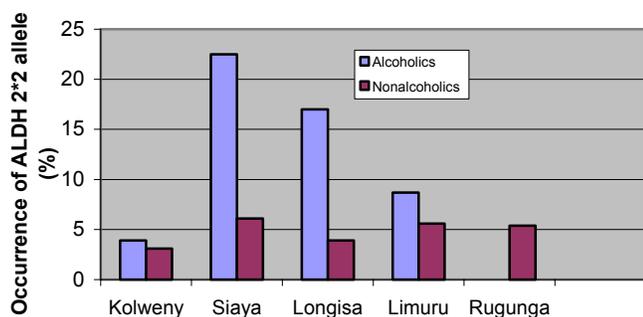


Figure 5. Occurrence of ALDH 2*2 allele among alcoholics and nonalcoholics* in the Kenyan populations.

*Nonalcoholics are alcohol drinkers without symptoms of alcohol dependence

DISCUSSION

Alcohol intake alone could not explain difference in the spread of alcoholism in the Kenyan study groups (Figure 2). Although alcohol consumption in all studied groups was exceeded the recommended safe dose of alcohol intake (Pequignot et al., 1978) the occurrence of alcohol

dependence in the Kenyan populations was apparently different (Figure 1). Protective properties of ADH 2*2, ADH 3*1 and ALDH 2*2 alleles against alcoholism were reported for some Asian populations (Thomasson et al., 1991; Chen et al., 1999; Peng et al., 1999). This hypothesis was tested for alcohol drinkers in the five Kenyan populations.

At the ADH 2 locus, alcoholics of the Limuru and Rugunga populations had significantly lower frequency of ADH 2*2 allele in comparison to nonalcoholics and therefore, protective properties of ADH 2*2 allele could be confirmed as similar to the report for Asian populations (Figure 3). In the Kolweny, Siaya and Longisa populations we observed the opposite as alcoholics had significantly higher occurrence of ADH 2*2 allele in comparison to nonalcoholics (Figure 3). At the ADH 3 locus in all Kenyan studied groups, alcoholics and nonalcoholics did not differ significantly in ADH 3 polymorphism (Figure 4). The occurrence of ALDH 2*2 allele among alcoholics and nonalcoholics in the Kenyan populations did not confirm the hypothesis of protective properties of this allele against excessive alcohol drinking and alcoholism. In contrary, alcoholics of the Longisa and Siaya populations had higher occurrence of ALDH 2*2 allele in comparison to nonalcoholics, although the level of significance reached only for the Longisa study group (Figure 5). It seemed that other factors than ADH 2, ADH 3 and ALDH 2 polymorphisms could contribute at defying the mechanism of protection by ADH 2*2, ADH 3*1 and ALDH 2*2 alleles against excessive alcohol drinking. In our study it was observed that ADH 2*2 and ALDH 2*2 allele carriers were mainly involved in alcohol drinking episodically or very seldom. Excessive alcohol drinking and preference of concentrated alcoholic drinks by alcoholics could interfere in metabolic protective role of ADH and ALDH alleles.

The analysis of ADH 2, ADH 3 and ALDH 2 polymorphisms indicated that genetic set up of ethanol metabolizing enzymes could not merely explain such large differences in the spread of alcoholism among the Kenyan communities. Therefore other factors than ADH and ALDH polymorphisms should be considered for further research to explain the difference in the spread of alcoholism in the Kenyan populations.

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