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Short communications

Distribution of ADH_2 and ALDH2 genotypes in different populations

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Summary. The distribution of the human liver alcohol dehydrogenase, ADH_2, and aldehyde dehydrogenase, ALDH2, genotypes in 21 different populations comprising Mongoloids, Caucasoids, and Negroids was determined by hybridization of the amplified genomic DNA with allele-specific oligonucleotide probes. Whereas the frequency of the ADH_2^1 allele was found to be relatively high in the Caucasoids, Mexican Mestizos, Brazilian Indios, Swedish Lapps, Papua New Guineans and Negroids, the frequency of the ADH_2^2 gene was considerably higher in the Mongoloids and Australian Aborigines. The atypical ALDH2 gene ($ALDH2^2$) was found to be extremely rare in Caucasoids, Negroids, Papua New Guineans, Australian Aborigines and Aurocanians (South Chile). In contrast, this mutant gene was found to be widely prevalent among the Mongoloids. Individuals possessing the abnormal ALDH2 gene show alcohol-related sensitivity responses (e.g. facial flushing), have the tendency not to be habitual drinkers, and apparently suffer less from alcoholism and alcohol-related liver disease.

Introduction

The occurrence of genetically determined atypical forms of human liver alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) has been reported in many populations (Agarwal and Goedde 1990a, b; Goedde and Agarwal 1987, 1989). The atypical ADH_2 gene is predominant among Mongoloids but is less common in Caucasoids and Negroids. Likewise, whereas about 50% of Japanese and Chinese liver autopsies and hair root follicles show a lack of the catalytic activity of the mitochondrial ALDH2 isozyme (designated as ALDH I in earlier publications), this isozyme abnormality has been detected in almost none of the Caucasoid, Negroid, and Aboriginal populations examined so far (Goedde et al. 1979, 1986; Goedde and Agarwal 1989).

Compared with Caucasoids, a significantly greater percentage of Orientals respond to a mild dose of ethanol with marked adverse reactions, such as facial flushing, increase of heart rate, hot feeling in the stomach, palpitations, tachycardia, and muscle weakness (Wolff 1972). The biochemical basis of the Oriental flushing has been shown to be caused by the genetically determined polymorphism of ALDH2. The inactive enzyme is responsible for elevated blood acetaldehyde levels leading to flushing symptoms (Agarwal and Goedde 1990a, b; Goedde and Agarwal 1987, 1989). These adverse responses are thought to discourage the use and abuse of alcohol in many ethnic and racial groups. However, little is known about the incidence of this "Oriental type" of facial flushing and related symptoms among non-Mongoloid populations. In a recent report (Peters et al. 1990), Caucasian subjects exhibiting alcohol-related flushing have been found to possess inherited defects in the ALDH1 isozyme.

In the present study, we have examined the distribution of ADH_2 and ALDH2 genotypes in different racial and ethnic groups comprising Caucasoids, Mongoloids, native Americans, Negroids, Papua New Guineans, Australian Aborigines, and some other population subgroups

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by using enzymatically amplified human genomic DNA followed by hybridization with appropriate allele-specific oligonucleotide probes.

Materials and methods

The blood samples of unrelated male and female subjects of various racial and ethnic origins were received in Hamburg as whole blood samples, blood spots dried on filter paper, isolated lymphocytes, or isolated DNA samples. Blood DNA was isolated using standard methods. For the genotyping of ADH_2 and ALDH2, allele specific oligonucleotide probes and enzymatic amplification by the polymerase chain reaction (PCR) were used as described before (Goedde et al. 1989; Singh et al. 1989; Meier-Tackmann et al. 1990). All genotype analyses were carried out in Hamburg.

Results and discussion

Until recently, it has only been possible to determine the phenotypes of the ADH_2 and ALDH2 polymorphic forms by means of electrophoretic and kinetic measurements using sources such as hair root follicles, organ biopsy and autopsy material (Goedde et al. 1979, 1986, 1989). The newly developed genotyping methods enable both homozygotes and heterozygotes for the ADH_2 and ALDH2 alleles to be unambiguously identified in blood samples, thus eliminating the need for organ biopsies and hair root follicles.

The distribution of the ADH_2 and ALDH2 genotypes and the frequencies for the respective alleles in various populations, grouped according to their racial origin, is shown in Table 1. Whereas the frequency of the ADH_2^1 allele was found to be relatively high in Caucasoids, Mestizos, Brazilian Indios, Swedish Lapps, Papua New Guineans and Negroids, the frequency of the ADH_2^2 gene was considerably higher in Mongoloids and Australian Aborigines than in the other populations studied. In Asian Indians, Caboclos and Turks, the frequency of the ADH_2^2 gene was also higher than that observed among the Caucasoids, Negroids and other populations. The atypical ALDH2 gene ($ALDH_2^2$) was found to be extremely rare in Caucasoids, Negroids, Papua New Guineans, Australian Aborigines and Aurocanians (South Chile). In contrast, this mutant gene was found to be widely prevalent among individuals of the Mongoloid race.

The ADH_2 and ALDH2 genotype distribution data obtained in the present study support our earlier findings that were based upon the phenotyping technique (Goedde et al. 1979, 1986). In addition, the present study reports, for the first time, the distribution of the genotypes for the ADH_2 and ALDH2 alleles (homozygote normal, heterozygote, and homozygote atypical) in a large num-

Table 1. Distribution of ADH_2 and ALDH2 genotypes in different populations

Population	ADH_2						ALDH2					
	n	Genotype			Gene frequency		*n*	Genotype			Gene frequency	
		1–1	1–2	2–2	ADH_2^1	ADH_2^2		1–1	1–2	2–2	$ALDH_2^1$	$ALDH_2^2$
Caucasoids												
Germans	233	214	19	0	0.959	0.041	193	193	0	0	1	
Swedes	90	89	1	0	0.994	0.006	99	99	0	0	1	
Finns	85	83	2	0	0.988	0.012	100	100	0	0	1	
Hungarians	115	103	12	0	0.948	0.052	117	114	3	0	0.987	0.013
Turks	44	34	9	1	0.875	0.125	57	57	0	0	1	
Indians	167	142	17	8	0.901	0.099	179	173	5	1	0.980	0.020
Mongoloids												
Chinese	86	7	41	38	0.320	0.680	132	92	38	2	0.841	0.159
Japanese	32	5	16	11	0.406	0.594	53	29	23	1	0.764	0.236
Koreans	177	7	55	115	0.195	0.805	218	156	58	4	0.849	0.151
Thais	111	51	46	14	0.667	0.333	111	100	11	0	0.950	0.05
Filipinos	57	11	23	23	0.395	0.605	86	85	1	0	0.994	0.006
Malays	65	11	31	23	0.408	0.592	73	68	5	0	0.966	0.034
Negroids												
Africans	37	37	0	0	1		49	49	0	0	1	
Other populations												
Caboclos (Brazil)	20	18	0	2	0.900	0.100	23	15	8	0	0.826	0.174
Aurocanians (South Chile)	27	27	0	0	1		7	7	0	0	1	
Mestizos (Mexico)	57	51	6	0	0.947	0.053	61	61	0	0	1	
Papua New Guineans	204	179	22	3	0.931	0.069	242	240	2	0	0.996	0.004
Australian Aborigines	22	10	9	3	0.659	0.341	37	37	0	0	1	
Swedish Lapps	100	99	1	0	0.995	0.005	100	100	0	0	1	
Eskimos (Alaska)	27	27	0	0	1		27	27	0	0	1	

ber of diverse populations, hitherto unknown regarding their ADH_2 and ALDH2 genotype constitution.

Although the majority of the flushers were genotypically atypical for the ALDH2 loci, the atypical ADH_2^2 gene may also account for some of the flushing cases, as suggested by Thomasson et al. (1990). A markedly lower incidence of ALDH2 isozyme abnormality has been observed in alcoholics than in psychiatric patients, drug dependents and healthy controls in Japan, China, Korea, and Taiwan (Harada et al. 1985; Yeh et al. 1989; Yamashita et al. 1990; Hwu et al. 1991). Moreover, a significantly lower number of patients with alcoholic liver disease have the ALDH2 deficiency gene (Shibuya and Yoshida 1988). The present study and the results from previous reports suggest that individuals possessing an atypical ALDH gene are sensitive to alcohol, tend to be discouraged from drinking excessive alcohol, and consequently have a lower risk of developing alcohol-related disorders.

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