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Alcohol Dehydrogenase and Alcohol Dependence: Variation in Genotype-Associated Risk between Populations

To the Editor:

Osier et al. (2002) report that haplotyping of the alcohol dehydrogenase (*ADH*) gene cluster at 4q21-23 showed unusually high values for F_{st}, an estimator of population differentiation. This was largely due to differences between populations in East Asia and those in other areas of the world. The finding was discussed in relation to the origin and maintenance of the distinct East Asian haplotype and in relation to possible association between genetic variation at this locus and the risk of alcohol dependence (MIM 103780). This letter draws attention to a potentially related difference between populations, in the magnitude of the alcohol dependence risk associated with the *ADH1B* (MIM 103720) Arg47His polymorphism (previously referred to as "*ADH2*2*"). One possible explanation for such a difference in risk is the presence of linkage disequilibrium between this marker and an undiscovered causative polymorphism, with the effect being stronger in East Asians and the relative risk associated with *ADH1B* Arg47His variation consequently being greater.

To update a previous meta-analysis of the effects of *ADH* polymorphisms (Whitfield 1997), articles reporting on *ADH1B* genotypes in control and alcohol-dependent subjects were identified by Medline search or from knowledge of data in conference proceedings, with elimination of articles in which subjects overlapped. Data from eight of the articles previously analyzed (all those listed in table 1 and published before 1997) and from nine new articles, were included. Information on *ADH1B* Arg47His genotypes in control and alcohol-dependent subjects was extracted. Data on alcohol-dependent subjects with known liver disease were excluded, because of the possibility that *ADH1B* variation may affect the risk of liver damage in alcoholics. Odds ratios were calculated from stratified 2 × 2 tables, using StatXact 5 (Cytel Software), with tests for heterogeneity across studies and estimation of common odds ratios. Whenever possible, two 2 × 2 tables were compiled from each article: one for the *ADH1B**47Arg/*47Arg versus *ADH1B**47Arg/*47His genotype comparison and the second for comparison of *ADH1B**47Arg/*47His against *ADH1B**47His/*47His.

Data from each article, exact odds ratios, and their 95% CIs are shown in table 1. For the *ADH1B**47Arg/*47Arg versus *ADH1B**47Arg/*47His (*ADH2*1/*1* versus *ADH2*1/*2*) comparison, there was significant heterogeneity of odds ratios across all the studies ($P < .0001$). Division of studies into those from Europe (including Russia and Australia) and those from Asia, with separate analyses for the two groups, showed no evidence of within-group heterogeneity among Europeans ($P = .397$), and the estimated common odds ratio was 2.11 (95% CI 1.32–3.44). However, there was still significant heterogeneity ($P < .0001$) among Asian studies. Inspection of the data suggested that results from Japanese and from Han Chinese groups were similar, whereas the minority ethnic groups within China, as well as Koreans, had lower odds ratios. As can be seen in table 1, the Han Chinese and the Japanese groups had very similar common odds ratios associated with *ADH1B**47Arg/*47Arg compared with *ADH1B**47Arg/*47His, which were substantially above those for Europeans and most of the other Asian groups.

The calculated odds ratios for *ADH1B**47Arg/*47His against ADH1B*47His/*47His (*ADH2*1/*2* versus **2/*2*) are also shown in table 1. There was no significant heterogeneity between studies ($P = .405$), and the estimated common odds ratio was 1.43 (95% CI 1.23–1.66). The difference in alcohol-dependence risk is therefore greater for *ADH1B**47Arg/*47Arg versus *ADH1B**47Arg/*47His than for *ADH1B**47Arg/*47His versus *ADH1B**47His/*47His, at least in the mainly East Asian populations in which the *ADH1B**47His allele frequency is high enough to allow a meaningful comparison.

Two conclusions may be drawn from this summary of published results. First, the *ADH1B**47His allelic effects on alcohol dependence risk are not additive. Heterozygotes are clearly more similar in risk to the *ADH1B**47His/*47His homozygotes than to the *ADH1B**47Arg/*47Arg homozygotes, and so the *ADH1B**47His allele shows quantitative (but not complete) dominance. Proposed mechanisms for the *ADH1B* Arg47His effect on dependence need to account for this

Table 1

Calculated Odds Ratios and Associated 95% CI for Alcohol Dependence by *ADH1B* Genotype

Population, Reference, and Sources of Subjects	Control Subjects			Alcoholics			RR vs. RH		RH vs. HH	
	RR	RH	HH	RR	RH	HH	OR	95% CI	OR	95% CI
Europeans:										
Gilder et al. 1993:										
England[a]	77	7	0	76	6	0	1.15	.32–4.35	NA	NA
Espinos et al. 1997:										
Spain	58	12	1	62	9	0	1.42	.51–4.13	NA	NA
Whitfield et al. 1998:										
Australia[b,c]	101	18	0	36	1	0	6.37	.94–274.60	NA	NA
Borras et al. 2000:										
France, Germany, Poland, Spain, Sweden[d]	214	10	0	226	5	0	2.11	.64–7.99	NA	NA
Ogurtsov et al. 2001:										
Russia (Moscow)[d]	15	29	6	24	12	1	3.80	1.39–10.94	2.44	.25–123.4
Frenzer et al. 2002:										
Australia [c,d]	184	14	2	54	3	0	1.37	.36–7.70	NA	NA
Common OR (all Europeans)							2.11	1.32–3.44	NA	NA
Asians:										
Thomasson et al. 1994:										
China (Atayal, Taiwan)	1	10	54	3	28	63	1.07	.08–61.93	2.39	1.01–6.03
Muramatsu et al. 1995:										
China (Han Chinese, Shanghai)	12	43	50	13	8	11	5.66	1.72–20.00	.85	.27–2.56
Chen et al. 1996:										
China (Han Chinese, Taipei)	0	19	44	14	15	17	NA	NA	2.03	.77–5.37
Shen et al. 1997:										
China (Han)	6	19	23	10	25	17	1.26	.34–5.03	1.77	.69–4.63
Korean	3	23	24	9	17	29	3.95	.82–26.11	.62	.25–1.51
Mongolian	6	14	15	11	15	5	1.69	.43–7.20	3.14	.80–14.10
Elunchun	12	22	3	13	15	3	1.58	.51–4.99	.69	.08–5.85
Osier et al. 1999:										
Taipei										
Han	6	56	73	40	39	49	9.42	3.52–29.86	1.04	.58–1.86
Ami	1	5	14	3	6	11	2.36	.13–156.6	1.51	.29–8.14
Atayal	0	7	13	0	6	15	NA	NA	.75	.16–3.38
Yin and Agarwal 2001:										
China (Han Chinese, Taipei)[e]	54	242	361	152	130	137	5.22	3.54–7.79	1.42	1.05–1.91
Higuchi 1994:										
Japan	31	152	247	204	224	227	4.46	2.86–7.10	1.60	1.21–2.13
Maezawa et al. 1995:										
Japan	2	22	36	30	28	38	11.48	2.45–109.90	1.20	.55–2.64
Nakamura et al. 1996:										
Japan	3	54	40	21	20	12	18.25	4.73–106.00	1.23	.50–3.11
Tanaka et al. 1996:										
Japan[d]	4	24	38	27	42	21	3.81	1.13–16.77	3.14	1.43–7.04
Lee et al. 2001:										
Seoul, Korea[d]	6	18	40	3	21	28	.44	.06–2.40	1.66	.70–3.98
Common OR:										
Han Chinese							5.19	3.74–7.26	1.36	1.07–1.72
Japanese							5.50	3.75–8.22	1.70	1.34–2.17

Note.—RR = *ADH1B**47Arg/*47Arg; RH = *ADH1B**47Arg/*47His; HH = *ADH1B**47His/*47His, OR = odds ratio, NA = Not applicable (odds ratio could not be calculated because of empty cells).

[a] U.K. or Irish descent.

[b] Men only.

[c] Australians of European descent.

[d] Control subjects versus alcoholics without alcoholic cirrhosis or pancreatitis.

[e] *ALDH2**11 and *12 subjects only.

feature. It is worth pointing out that a study that measured hepatic ADH activity and *ADH1B* genotype in human livers found that activity at pH 7.5 was approximately fivefold higher in *ADH1B**47Arg/*47His subjects and was only sixfold higher in *ADH1B**47His/*47His subjects than in those with the *ADH1B**47Arg/*47Arg genotype (Yao et al. 1997). It is not clear whether these two examples of nonadditive effects of this polymorphism are related.

Second, there was a notable difference between European and Chinese or Japanese risk estimates. At least two types of explanation for heterogeneity between populations in the relative risk conferred by, or associated with, a genetic polymorphism should be considered: genetic and social. If the polymorphism is not itself causative, then linkage disequilibrium with a causative locus will decrease with the passage of time after the original mutation event and may remain stronger in one group

than in another. Alternatively, the same neutral polymorphism may have arisen independently in the two populations and may be in linkage disequilibrium with the causative polymorphism in only one. It will be seen from table 4 in the article by Osier et al. (2002) that the *ADH1B**47His allele occurs on a different haplotype background in East Asians (mainly 221221) and the European/Middle Eastern/European North American groups (mainly 221211, or 212211 in some Samaritans). Although this does not demonstrate independent mutations, it does suggest that the origin of *ADH1B* Arg47His is not recent and that changes have occurred in the nearby sequence.

It has generally been assumed that the *ADH1B* Arg47His polymorphism is causative and that the effect arises from the difference in V_{max} for ethanol (Bosron and Li 1986) between the enzymes produced. However, there are problems in extrapolating this in vitro activity difference to alcohol metabolism in vivo, and as Osier et al. (1999, 2002) discuss, another causative polymorphism within the *ADH* region cannot be excluded.

On the other hand, social factors or other unlinked genetic effects may modify the *ADH1B* Arg47His effect in the comparatively few Europeans who have the *ADH1B**47Arg/*47His or *ADH1B**47His/*47His genotypes, so the genotype-associated difference in risk is smaller. There is evidence (Higuchi et al. 1994) that the size of the protective effect associated with aldehyde dehydrogenase (ALDH2) deficiency has changed during the past 20 years in Japan—a period that, although it is far too short for genetic changes, has been a time of substantial alterations in the social environment. Lee et al. (2001) also comment on the social pressures to drink in Korea. Gene-environment interaction therefore presents an alternative explanation for the heterogeneity between populations.

We cannot yet determine whether social factors or variations in linkage disequilibrium are responsible for the difference in *ADH1B* Arg47His effects between Europeans and two major Asian groups. The question may be resolved by haplotype data across the *ADH* region in alcoholics and control subjects from different countries or regions, or by studies of alcoholics and control subjects of Asian descent living in European societies.

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Electronic-Database Information

Accession numbers and the URL for data presented herein are as follows:

Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/Omim/ (for ADH1B [MIM 103720], alcoholism [MIM 103780], and ALDH2 [MIM 100650]

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Reply to Whitfield

To the Editor:

Dr. John B. Whitfield (Whitfield 2002 [in this issue]) writes to call attention to the variation in alcohol-dependence risk as a function of both the *ADH1B* Arg47His polymorphism *and* specific populations. We do not disagree with his result: our study (Osier et al. 2002) involved, primarily, normal individuals from multiple populations and showed considerable variation in allele frequencies at that site among the populations. In that report, we commented that the different risks of alcoholism associated with alleles at this site could be explained by other relevant variation on the specific haplotype at high frequency in eastern Asia. However, we did not show that haplotyping of the ADH Class I polymorphisms resulted in an unusually high F_{st} but that some individual sites in the gene cluster individually had unusually high F_{st} values. One particular haplotype does have a very large range of variation, but we do not have an appropriate empiric distribution for F_{st} values in multiallelic haplotype systems to show that it is unusually large. We showed that the "protective" allele, *ADH1B*47His,* occurs primarily on a specific haplotype in the Mediterranean and European populations studied but occurs on a different haplotype in eastern Asia. We concluded that the *ADH1B*47His* allele is likely to be old, a conclusion Whitfield reiterates.

We do disagree with some of the conclusions Whitfield reaches. He concludes that the effects of the *ADH1B*47His* allele are not additive. However, because of the strong linkage disequilibrium (LD) across the Class I gene cluster, Whitfield's analysis showing nonadditive allelic effects uses the *ADH1B*47His* allele as a surrogate for the entire haplotype. Those analyses do not provide sufficient evidence to limit the effect to just that allele; some other variant on that haplotype could be relevant. Taken together, the evidence that the risk difference associated with this polymorphism is not the same in Europe as it is in eastern Asia and our demonstration that the haplotype containing the *ADH1B*47His* allele is different in Europe from the one in eastern Asia require us to focus on the entire haplotype and not just on this one site. The nonadditive effects cannot be attributed to the *ADH1B*47His* allele exclusively, as Whitfield himself notes earlier in his introductory paragraph.

Whitfield repeats a common error when he says LD will decrease over time, without noting all of the assumptions involved in that deterministic result. In regions of high disequilibrium caused by very low levels of recombination, the effects of random genetic drift can easily outweigh the deterministic expectation, as we have demonstrated (Calafell et al. 2001). Modern humans have existed outside of Africa for a relatively short time and had small population sizes during much of that time. Thus, drift associated with the expansion out of Africa and diversification around the world can swamp any factors like recombination that tend to reduce LD. Since these ADH cluster genes are involved in alcohol metabolism, we of course have the additional complication of determining to what extent natural selection may have played a role in altering the frequency of particular haplotypes in different geographical regions.