Distribution of the Alcohol Dehydrogenase *ADH1B*47His* Allele in Eurasia

To the Editor: Recently, Li et al.[1] reported on the frequency of the derived allele *ADH1B*47His* in Eastern and Western Asia.

The data were based on meta-analysis of the published results for 131 populations and the results of genotyping of samples from 37 additional populations, performed by the authors. The authors made the suggestion that there had been separate and independent increases in the frequency of the *ADH1B*47His* allele in Eastern and Western Asia. Their worldwide-frequency-distribution diagram for this allele also includes the previous reports that there is a regional elevation in the *ADH1B*47His* allele for Eastern Europeans (Russians). The authors acknowledged that Central Asian population data that would support their conclusion about this distribution are, as yet, absent.

The allele-frequency data derived from the two previous studies[2,3] were essential for the hypothesis that a local maxima for distribution of *ADH1B*47His* might exist on the Russian Plain and in Southwest Asia.[1] We noted, however, that the frequencies of the *ADH1B*47His* allele presented in these studies for Russians[2] and Iranian populations[3] are significantly distinct from the allele frequency for the same or neighboring population groups reported in other studies.[4–7] There are several fairly obvious factors that could produce these differences: first, genotyping errors might occur, depending on methods that vary between the different studies; second, small (nonrepresentative) numbers of genotyped samples were included; third, genetic drift might occur in a local community enrolled in genotyping within the ethnic group of interest; fourth, there might have been recent undetected gene flow from a distant geographic region with a different frequency of the allele. There are reasonable concerns that errors in genotype data for some populations might affect the meta-analysis and the resulting conclusions regarding the evolution of this functionally significant polymorphism.

In this Letter, we elucidated the allele-frequency data for Russians and Southwest Asian populations and added data on Central Asian and Siberian populations to provide a complete description of the Eurasian distribution of the *ADH1B*47His* allele. We have typed the *ADH1B Arg47His* polymorphism for 3408 individuals in 46 additional populations by PCR-RFLP with *Msl*I using primers and protocols described eslewhere[4] and have developed a refined geographic map that includes 172 populations from Africa and Eurasia (Figure 1, Table 1).

As indicated by Li et al.,[1] "the Moscow Russian sample appears anomalous with a fairly high frequency (41%) of *ADH1B*47His*" resulting in a local maximum in the central part of the Russian Plain on the allele-frequency map (Figure 2 in Li et al.[1]). In addition, in another study,[8] the frequency of the allele for Russians in Siberia was also found to be relatively high (~20%), which is significantly different from other European populations. To estimate the frequency among Russians more extensively, we have carried out further genotyping in Muscovites and in other Russian populations from different geographic regions (Table 1). The frequency of the *ADH1B*47His* allele in Russians across the country (including both European and Asian parts of Russia) varies between 1.9% and 7.6%, with a mean frequency of 4.9% in the total group of 1019 Russian individuals. These data agree with other data on *ADH1B*47His* allele frequency for Northern Russian populations of Archangelsk (5%)[9] and Vologda (6%)[4,] and are similar to the frequencies that we estimated for the closest relative Slavic groups (Ukrainians and Byelorussians; see Table 1). The higher frequencies of the allele reported previously for Russians[2,8] are, therefore, most likely the result of genotyping error. In support of such an explanation, a significant deviation in Hardy-Weinberg equilibrium is observed in at least one of these studies ($p < 0.001$).[8]

A second study[3] used by Li et al. for their comparative allele-frequency estimation in Western Asia shows that the frequency of *ADH1B*47His* in Iran is also relatively high (46% in Turks from Iran, 68% in Persian Zoroastrians from Iran, and 51% in Turkmen from Northeastern Iran bordering Turkmenistan) compared with the main part of other populations from the same geographic area. Again, potential errors in genotyping may also be suspected, given that an excess of heterozygotes and significant deviation from Hardy-Weinberg equilibrium was observed in this study.[3] The methods used in these studies, such as PCR-RFLP with *Mae*III[2,8] or amplified product-length polymorphism assay,[3] could potentially contribute to genotyping errors. Because *ADH1B*, *ADH1A*, and *ADH1C* are highly homologous genes, the genotyping requires highly specific PCR primers for the *ADH1B* gene. We previously genotyped a limited number of individuals from Iran and found a significantly lower frequency of the allele (24%),[5] a value that is close to the allele frequency in another population in the region (Druze, 27%).[4] We have also tested samples from Southern Turkmen native to a region bordering Northern Iran and found a similar frequency (20.4%). Given the *ADH1B*47His* frequency in Turks that was reported earlier (12.5%),[7] the general frequency of the allele in Western Asia is at least 2- to 3-fold lower than that in the data from the literature used by Li et al.[1] for the estimation of geographic distribution. The Samaritans are another population group from Southwest Asia who have a very high frequency of the

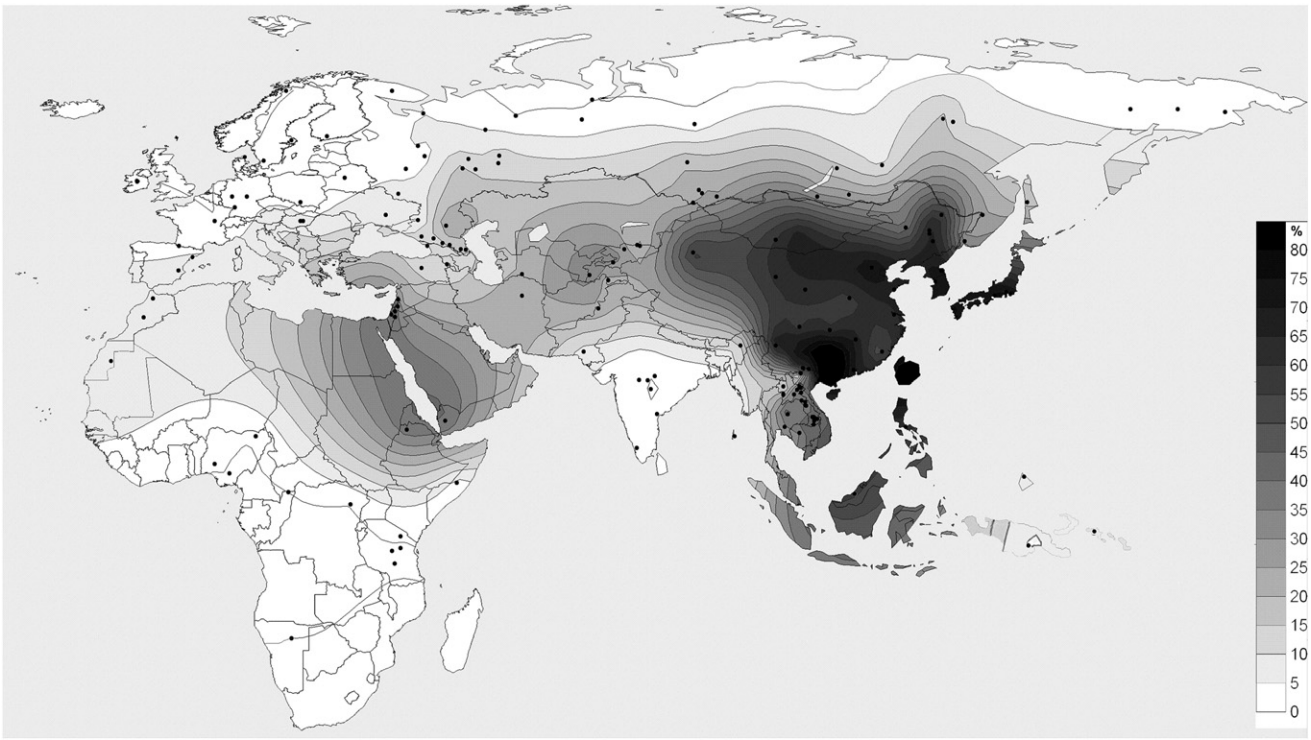

Figure 1. The Geographic Distribution of the *ADH1B*47His* Allele
The frequency data and geographic coordinates for populations under study (Table 1), added to the frequency data and geographic coordinates for 126 populations published by Li et al.[1] and ALFRED. Surface Mapping System program Surfer 8.00 (Golden Software) was used.

allele and were also employed in their analysis.[1,4] They are a genetic isolate with an apparent bottleneck in their recent evolutionary history, which results in marked genetic differences between Samaritans and other populations in the region.[10,11] In other Southwest Asian groups, Yemenites and Sephardic Jews, the frequency of the allele reached a maximum of 41%,[4] with an average frequency ~30% in this region. The mean is much lower than that used for genogeography reconstruction.[1]

To estimate the detailed geographic distribution of the *ADH1B*47His* allele, we genotyped 23 populations across Asia, including Central Asian populations (Table 1). The overall allele frequencies in Southwestern Asia were relatively close to those in Central Asia (~19%–32%). Thus, the discontinuity between West and East Asia seems to be less pronounced than previously suggested[1] (Figure 1).

As was shown, Southeast Asia has the highest recorded allele frequency (70% and higher), whereas South Asia as a whole has a relatively low frequency of the *ADH1B*47His* allele (~10% or lower).[1,4,7,12] According to our data, the Southwest Asian local maximum reaches 30% frequency and is connected with the Southeast Asian maximum via the Asian steppe belt, where the average allele frequency is ~20%–30%. The frequency from the steppe region toward the North and West reduces gradually in the range of ~10%–16% in populations across the Caucasus and Volga-Ural regions. The only exception is the Kalmyk population (26.3%), with ancestor roots from Mongol-Oirat tribes, who migrated to this region from Central Asia approximately 300 years ago. This frequency is similar to those in other related Mongoloid groups (Altaians and Buryats) (Table 1) and might reflect a relatively high frequency of the allele in ancestor Mongoloid groups in Central Asia.

This wider distribution might be explained by the migration processes in the Asian steppes. More extensive data must now be collected for *ADH*-locus haplotype analysis in different ethnic populations to elucidate whether the geographic frequency of the *ADH1B*47His* allele is indeed increased separately; i.e., to see whether it is under direct differential selection pressure in different ethnic groups or whether the observed pattern reflects migration processes in Asia and nearby European regions.

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Table 1. Populations Sampled in This Study

Country	Population	Latitude	Longitude	N	Number of Genotypes			ADH1B*47His Frequency (%)
					Arg/Arg	*Arg/His*	*His/His*	
Russia	Russians (Kostroma)[a]	57.8 N	40.9 E	118	111	7	0	3.0
Russia	Russians (Kursk)	51.7 N	36.2 E	86	73	13	0	7.6
Russia	Russians (Rostov district)	47.3 N	39.8 E	96	88	8	0	4.2
Russia	Russians (Moscow)	55.8 N	37.6 E	104	100	4	0	1.9
Russia	Russians (Bashkortostan)	54.7 N	56.0 E	99	94	5	0	2.5
Russia	Russians (Siberia)[b]	84.9 N	56.4 E	487	429	58	0	6.0
Russia	Russians (Chukotka)	64.7 N	177.5 E	29	25	4	0	6.9
Ukraine	Ukrainians[a]	48.0 N	34.0 E	109	91	18	0	8.3
Belarus	Byelorussians	54.0 N	27.0 E	126	119	7	0	2.8
Russia	Kola Saami	68.0 N	35.0 E	62	57	5	0	4.0
Russia	Komi-zyrians	61.4 N	50.8 E	49	44	5	0	5.1
Russia	Maris	57.0 N	48.0 E	98	77	20	1	11.2
Russia	Udmurts (Purga)	56.3 N	53.0 E	68	51	17	0	12.5
Russia	Udmurts (Igra)	57.9 N	53.3 E	94	75	16	3	11.7
Russia	Tatars	55.6 N	49.3 E	21	16	5	0	11.9
Armenia	Armenians	40.1 N	44.5 E	39	32	6	1	10.3
Russia	Ingush	43.2 N	44.8 E	47	33	13	1	16.0
Russia	Darginians	42.4 N	47.5 E	49	36	13	0	13.3
Russia	Avars	42.5 N	46.7 E	50	33	15	2	19.0
Georgia	Abkhaz	43.0 N	41.0 E	50	41	8	1	10.0
Russia	Balkars	43.5 N	43.6 E	40	30	9	1	13.7
Russia	Cherkess	44.2 N	42.1 E	53	40	12	1	13.2
Russia	Kalmyks	46.3 N	44.2 E	59	30	27	2	26.3
Iran	Iranians[a]	35.0 N	57.0 E	41	24	14	3	24.4
Turkmenistan	Turkmen	38.8 N	57.0 E	54	35	16	3	20.4
Uzbekistan	Uzbeks	42.8 N	74.6 E	25	13	11	1	26.0
Kirghizia	Kirghizs	40.5 N	72.6 E	102	41	54	7	33.3
Tadjikistan	Tadjiks	38.6 N	68.8 E	60	23	32	5	35.0
Tadjikistan	Pamir mountain dwellers[a]	37.8 N	71.6 E	30	18	11	1	21.7
Kazakhstan	Kazakhs	43.3 N	76.6 E	35	22	12	1	20.0
Kazakhstan	Uyghurs	43.0 N	77.0 E	29	19	9	1	19.0
Russia	Altaians Northern	51.9 N	85.6 E	96	57	34	5	22.9
Russia	Altaians Southern	50.8 N	85.5 E	65	40	24	1	20.0
Russia	Tuvinians	50.9 N	90.1 E	51	29	18	4	25.5
Russia	Buryats (Ulan Ude)	51.8 N	107.6 E	118	65	43	10	26.7
Russia	Buryats (Kurumkan)	54.2 N	110.2 E	61	38	22	1	19.7
Russia	Buryats (Aginskoe)	51.1 N	114.3 E	65	34	29	2	25.4
Russia	Khants	63.7 N	67.1 E	145	143	2	0	0.7
Russia	Kets	62.5 N	86.2 E	51	49	2	0	2.0
Russia	Chukchi	64.9 N	176.0 E	45	43	2	0	2.2
Russia	Evenks (Eastern)	56.0 N	118.0 E	72	60	11	1	9.0
Russia	Yakuts	62.9 N	130.2 E	53	44	8	1	9.4
Russia	Siberian Tatars	56.4 N	84.5 E	75	48	25	2	19.3
Russia	Nivkhs	50.1 N	142.5 E	31	20	11	0	17.7
Russia	Udege	46.8 N	134.2 E	58	31	23	4	26.7
Russia	Nanais	44.0 N	132.0 E	13	8	3	2	26.9

No deviation from Hardy-Weinberg equilibrium was observed for the studied populations.
[a] partially published in Borinskaya et al.[5]
[b] partially published in Marusin et al.[6]

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Web Resources

The URL for data presented herein is as follows:

Allele Frequency Database (ALFRED), http://alfred.med.yale.edu/alfred

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Low Allele Frequency of *ADH1B*47His* in West China and Different *ADH1B* Haplotypes in Western and Eastern Asia

To the Editor: In their Letter to the Editor, Borinskaya et al.[1] provide valuable new data and comments on our previous paper[2] on the geographic distribution of the *ADH1B*47His* allele. They believe that some of the previously published data we included are anomalous and probably the result of typing errors. They present new data to support their conclusion. We agree with this, because the best way to identify anomalous or erroneous gene-frequency data is to type additional relevant population samples, as Borinskaya et al.[1] have done. The more comprehensive investigation in Central Asia, Siberia, and Eastern Europe by Borinskaya et al.[1] fills in the map of Asia by providing allele-frequency data on multiple population samples from a region that was insufficiently sampled at the time of our analysis.[2] With these new data, the discontinuous distribution of *ADH1B*47His* that we saw across Southern Asia has become a more continuous low-frequency distribution across Central Asia. With the previous Iranian data removed, the Southwestern Asian region of higher allele frequency is considerably reduced in extent and magnitude, though the frequency is still higher in populations bordering the Mediterranean and Red Seas than in the Central Asian populations.

In our recent publication on the ethnicity-associated positive selection on *ADH1B*47His* in Eastern Asia,[3] we published its allele frequency for additional populations, such as Uygur, Kazakh, Mongol, Khams, etc. There have also been other recent reports of *ADH1B*47His*-allele frequencies for more population samples.[4] In total, we have assembled data on 98 more population samples (72 from the literature and 26 from our lab) since our previous publications[2,3] (see Table S1, available online). The data on the 26 of those samples that we have typed are presented here (Table 1). These data show that the *ADH1B*47His* allele frequency decreases dramatically from East China to West China. On the Tibetan Plateau, the frequency is only around 5% (Khams, Amdo, and Tibetans in Table 1). The low-frequency area now clearly extends from Southern Asia to the Tibetan Plateau. In the Xinjiang Uyghur Autonomous Region of Northwest China, the frequency is around 20%[3], similar to what Borinskaya et al[1]. have found farther west and considerably lower than the high frequency in East China (around 70%).[3,4]

We have also collected new data that demonstrate that some parts of Southwestern Asia are a region of higher frequency than those more Central Asian regions. Even if we remove the data for the Samaritans, which our extensive genetic data confirm have undergone significant genetic drift,[5] a region of higher frequency is still evident