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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

Table 1. *ADH1B*47His* Allele Frequency of Some Newly Typed Populations

Country	Population	2N	*ADH1B*47His* Frequency (%)	Longitude	Latitude
China	Khams-Qamdo	192	2.60	97.1E	31.1N
China	Amdo-Qinghai	172	3.49	98E	35N
China	Tibetan-Xigazê	144	4.86	88.8E	29.2N
China	Tibetan-Lhasa	144	6.94	91.1E	29.7N
China	Daur	42	30.95	124.5E	48.5E
China	Hezhen	40	27.50	134E	48N
China	Korean-Jilin	78	42.31	126.5E	43.9N
China	Manchu	46	50.00	127.5E	49.5N
China	Mongol-Hulunbel	34	29.41	119.7E	49.2N
China	Xibo-Kaiyuan	24	16.67	124.0E	42.5N
China	Han-Anyang	44	70.45	114.3E	36.1N
China	Shē-Jingning	78	78.21	119.5E	27.8N
China	Han-Putian	30	80.00	119.0E	25.5N
China	Han-Minnam	38	92.11	118.6E	24.8N
China	Han-Teochow	160	73.13	116.4E	23.5N
Vietnam	Vietnamese-Huê	22	68.18	107.5E	16.5N
Malaysia	Malaysians	22	9.09	102E	3N
India	Thoti	28	0.00	79E	19N
Kuwait	Kuwaiti	32	9.38	48E	29N
Israel	Palestinian Arabs[a]	140	15.71	35.3E	32N
Greece	Greek	104	20.19	23E	38N
Italy	Roman Jews	52	26.92	12.5E	41.8N
Italy	Sardinian	68	4.41	9E	40N
Italy	Toscani	172	4.07	11E	43.5N
Zaire	Lisongo	16	0.00	21.5E	3N
Columbia	Guihiba	24	0.00	69.5W	5.8N

[a] These samples were obtained from the National Laboratory for the Genetics of Israeli Populations, Tel Aviv University, Israel.

in Southwestern Asia. The frequency is always higher in the Jewish populations (Ethiopia, 38%; Yemen, 41%; Central and Eastern Europe, 27%; Italy, 26%, and the Sephardim, 41%) and the Druze population (27%) than in the Arab populations (Palestinian, 15.7%; Kuwaiti, 9.4%). Moreover, the high genetic drift in Samaritans does not bias the allele frequencies and one can argue that their allele frequency is relevant. There appears to be a higher allele frequency in the populations that originated in the Levant than exists farther north and east. We are regularly updating the collection of *ADH1B*47His* allele frequencies for different population samples in ALFRED, the online open-access database of allele frequencies for molecularly defined polymorphisms in anthropologically defined population samples (see Web Resources). The data from our lab and the newly published data are already being entered. When the frequency data assembled by Borinskaya et al.[1] are entered, the number of population samples typed will be > 300, making the global distribution of this SNP one of the most comprehensive.

In their closing, Borinskaya et al.[1] note that haplotype analyses will be important in the future. We agree and have already published some data showing that the haplotypes with the derived *ADH1B*47His* allele are different in Eastern Asia from those in Western Asia.[3] In that paper, we showed that in the Samaritans, the Druze, and the Ashkenazi Jews, the *ADH1B*47His* allele occurred on two haplotypes that were not seen in Far Eastern Asia. We now have haplotype data for those same six SNPs—rs2066701, rs2075633, rs4147536, rs1229984 (Arg47His), rs6810842, rs3811801—in additional Southwestern Asian and Eastern European populations. The haplotypes common in these western populations are GACAGG and GAAATG (hereafter W1 and W2) and are quite different from those in Eastern Asia, >AGCAGG and AGCAGA (hereafter E1 and E2). E2 is obviously derived from E1, which is common only in Eastern Asia. However, we can now show (Li et al., unpublished data) that populations such as the Adygei and Chuvash have both E2 and W1, with both occurring in the 6%–13% range.[6] E2 showed strong evidence of selection on the basis of the long-range haplotype test, but only in some populations.[3,7] Preliminary analyses of short-tandem-repeat polymorphism data have also indicated that E2 is younger than W1.[6] This emphasizes the importance of haplotypes of the Central Asian populations being studied by Borinskaya et al.[1] for a fuller understanding of the historic patterns of the spread of this allele and of the roles that demography and selection have played.

The developing geographically detailed picture of the frequencies of the *ADH1B*47His* allele and the haplotypes on which it occurs will serve as a model for understanding human expansions and migrations, as well as the geographic and cultural influences upon genotypes that affect disease susceptibility and natural selection. It will take the efforts of many researchers and laboratories to complete the picture.

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Supplemental Data

Supplemental Data include one table and can be found with this article online at http://www.ajhg.org/.

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Web Resources

The URL for data presented herein is as follows:

ALFRED, http://alfred.med.yale.edu

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