have been affected by their sparse population coverage. The median line of the Eurasian genetic landscape appears to lie to the west of the Xinjiang Uyghur Autonomous Region of China. When we have collected more data on these 34 populations, we should be able to refine these estimates.

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Supplemental Data

Supplemental Data include one figure and one table and can be found with this article online at http://www.cell.com/AJHG.

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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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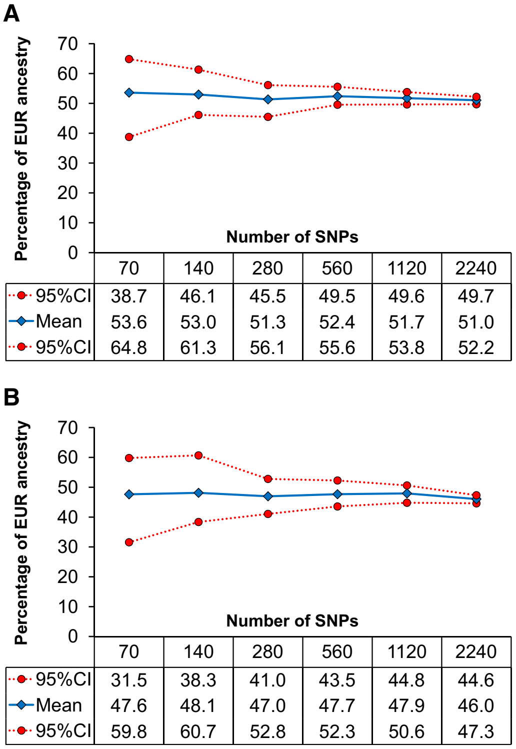
Response to Li et al.

To the Editor: Li et al. analyzed 68 SNPs genotyped on 1766 individuals from 34 populations and provided a lower estimation (31.2%) than ours (47%–52%)[1] of European genetic ancestry in Uyghurs. They argue that our estimation "may have been affected by sparse population coverage." The study of Li et al. is very interesting and provides some new insights into the genetic landscape of Eurasia. Here we show that the discrepancy between the two estimations could be attributable to either the difference in Uyghur samples per se, the variation of the estimation using a small number of markers by Li et al., or both.

In our study, we analyzed two Uyghur (UG) population samples, one from Yili, which is located in northern Xinjiang (hereafter referred to as N-UG), and the other from Hetian (or Hotan), located in southern Xinjiang (S-UG). Comparing the SNPs typed in Uyghur samples of Li et al. (Li-UG) and those in ours, 6 of 20 SNPs shared by Li-UG and S-UG and 3 of 6 SNPs shared by Li-UG and N-UG showed large allele frequency difference (>0.1). The average F_{ST}s between Li-UG and our Uyghur samples (0.0048 and 0.0094) are significantly larger than that between N-UG and S-UG (0.0009; see Table 1), suggesting that the Uyghur samples that Li et al. used could be rather different in genetic structure from ours. It is therefore not unexpected that the two studies give different estimations.

In addition, because Li et al. used only 68 random SNPs for ancestry estimation, we suspected that a substantial variation in estimations could be introduced by their small number of markers per se. Indeed, we noted in previous studies that the estimation of admixture proportion could vary in different marker panels even in the same population sample.[2,3] We conducted STRUCTURE analyses with a different number of SNPs that were randomly selected from genome-wide data in our previous study.[1] We found that as much as a 26% difference (the width of the 95% confidence interval) could be introduced in the genetic ancestry estimations when only 70 random SNPs were used (Figure 1), which is larger than the difference between the estimation of Li et al. (31.2%) and our estimation (47%–52%). It is clear that the variation of estimations decreases as the number of markers increases (Figure 1); for example, the difference was only 2.5% when 2240 SNPs were used, indicating that a considerable number of random markers are needed for a reliable estimation of genetic ancestry in an admixture population.



A

	70	140	280	560	1120	2240
● 95%CI	38.7	46.1	45.5	49.5	49.6	49.7
◆ Mean	53.6	53.0	51.3	52.4	51.7	51.0
● 95%CI	64.8	61.3	56.1	55.6	53.8	52.2

B

	70	140	280	560	1120	2240
● 95%CI	31.5	38.3	41.0	43.5	44.8	44.6
◆ Mean	47.6	48.1	47.0	47.7	47.9	46.0
● 95%CI	59.8	60.7	52.8	52.3	50.6	47.3

Figure 1. Estimation of the Percentage of European Ancestry in Uyghurs via Different Numbers of Markers

To estimate the European (EUR) ancestry in southern Uyghur (S-UG; A) and northern Uyghur (N-UG; B) populations, we used CEU and CHB (see text) as reference populations. For each given number of SNPs, 100 data sets with randomly selected markers were generated, and STRUCTURE analyses were performed with 20,000 iterations after a burn-in of length 30,000, with the admixture model and assuming that allele frequencies were correlated.

Furthermore, to exam the possible bias in estimation due to the selection of reference populations, we reanalyzed both the short tandem repeat (STR) and SNP data of a Human Genome Diversity Project panel that contained 940 unrelated individual samples collected from 52 worldwide populations. We ran STRUCTURE analysis for the 783 STRs[4] and 4600 randomly selected SNPs from Illumina HumanHap650K genome-wide data.[5] We found that the addition of more reference populations did not yield a significantly different estimation of European genetic ancestry in Uyghurs from those based on Utah residents with Northern and Western European ancestry from the CEPH collection (CEU) and Han Chinese from Beijing (CHB) populations in the HapMap study (see Figure S1 available online). In addition, via haplotype sharing analysis, a new method that we proposed recently,[6] we estimated that the contribution of European genetic ancestry to S-UG is 56%, which is very close to our previous estimation based on STRUCTURE analysis and the same Uyghur samples as well as the same data.[2]

Table 1. Pairwise F_{ST} between Uyghur Population Samples

	Li-UG	N-UG
N-UG	0.0048 ± 0.0047	
S-UG	0.0094 ± 0.0078	0.0009 ± 0.0004

Li-UG represents Uyghur samples used by Li et al.; N-UG represents Uyghur samples collected from northern Xinjiang (Yili); S-UG represents Uyghur samples collected from southern Xinjiang (Hotan). F_{ST} between Li-UG and N-UG was calculated based on allele frequencies of 6 overlapped SNPs; F_{ST} between Li-UG and S-UG was calculated based on allele frequencies of 20 overlapped SNPs; F_{ST} between N-UG and S-UG was obtained from Xu and Jin.[1] Standard deviation is shown for each pairwise F_{ST}.

In summary, our extended analyses suggest that the difference between the two estimations could be attributable to either the selection of different Uyghur population samples by Li et al. versus those that we used in our previous studies, the small number of markers that they used, which could introduce considerable variance in the estimation, or both. Regardless of the true cause of the discrepancy, the different estimations should prompt a close examination of the presence of a possibly substantial variation of admixture among Uyghur populations, a phenomenon similar to that observed in African Americans and Hispanics.

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Haplotype Background, Repeat Length Evolution, and Huntington's Disease

To the Editor: Warby et al.[1] present fascinating data on the haplotype background of chromosomes carrying the Huntington's disease (HD [MIM 143100]) mutation and the length distribution of the CAG repeat for different haplotypes within the general population. One of their conclusions is that *cis*-elements are likely to represent a major predisposing element in HD expansion. Here, I use evolutionary modeling of the CAG repeat length distribution within populations to argue that the distribution of CAG repeat length and disease incidence in different haplotypes can be explained by founder events, each of which involved expansion of repeats to lengths that are classified as normal by HD investigators (<28 repeats). There is therefore no need to invoke *cis*-element polymorphism within the human population.

Mutation of the HD CAG repeat is both upwardly biased (increases in repeat length are more frequent than decreases) and length dependent (longer repeats mutate more frequently than short ones). Based on sperm typing data, Falush et al.[2] estimated that the mutation rate was proportional to the number of repeats to the power of eight, so that, for example, alleles with 23 copies of the repeat would be approximately 10 times more mutable than alleles with 17 repeats, and alleles with 32 repeats would be approximately 100 times more mutable. The strong length dependence of the mutation rate means that CAG length in itself is a powerful factor in determining the stability of the repeat. Additionally, beyond approximately 55 repeats, the HD mutation causes juvenile HD, which makes further transmission impossible. In fact, the data argue that in modern populations, selection acts strongly against repeat lengths of 44 or more.[2]

I simulated the repeat length distribution in an infinite population based on the mutational model in Falush et al. In order to simulate the effect of natural selection, I removed all repeats of length 50 or more from the population. Simulations show that the assumptions made in modeling selection against disease alleles of different lengths have a negligible effect on the repeat length distribution among normal chromosomes (data not shown). In small populations, e.g., the early settlers of Europe, particular haplotypes can drift to high frequency, also increasing the frequency of the CAG repeat that they carry. In order to investigate the effect of founder events, the population was initially started with three haplotypes each at 1/3 frequency and with initial repeat lengths of 17, 23, and 32 (Figure 1).

A repeat of length 17 has a <0.2% chance of mutating in each generation, so that after 100 generations, most repeats of this length remained unchanged. A repeat of length 32 has a 20% chance within each generation. After 100 generations, most of the repeats of length 32 have mutated at least once, with a majority expanding to length 50 and being removed by natural selection. Consequently,