

Genome Scans of DNA Variability in Humans Reveal Evidence for Selective Sweeps Outside of Africa

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The last 50,000–150,000 years of human history have been characterized by rapid demographic expansions and the colonization of novel environments outside of sub-Saharan Africa. Mass migrations outside the ancestral species range likely entailed many new selection pressures, suggesting that genetic adaptation to local environmental conditions may have been more prevalent in colonizing populations outside of sub-Saharan Africa. Here we report a test of this hypothesis using genome-wide patterns of DNA polymorphism. We conducted a multilocus scan of microsatellite variability to identify regions of the human genome that may have been subject to continent-specific hitchhiking events. Using published polymorphism data for a total of 624 autosomal loci in multiple populations of humans, we used coalescent simulations to identify candidate loci for geographically restricted selective sweeps. We identified a total of 13 loci that appeared as outliers in replicated population comparisons involving different reference samples for Africa. A disproportionate number of these loci exhibited reduced levels of relative variability in non-African populations alone, suggesting that recent episodes of positive selection have been more prevalent outside of sub-Saharan Africa.

Introduction

Genetic and archaeological evidence suggest that the demographic history of anatomically modern humans involved a range expansion out of Africa approximately 50,000–150,000 years before present (BP) (Cavalli-Sforza, Menozzi, and Piazza 1994; Harpending and Rogers 2000; Relethford 2001; Excoffier 2002). The colonization of novel environments outside the ancestral species range likely entailed many new selection pressures caused by emergent infectious diseases, changes in diet, and exposure to new climatic conditions. Adaptive challenges posed by new biological, cultural, and physical environments were likely to have been particularly acute after the start of the Neolithic, 10,000 years BP, which marked the advent of agriculture and associated increases in population density. These considerations suggest that, within the last 10,000 years of human history, genetic adaptation to local environmental conditions may have been more prevalent in colonizing populations outside of sub-Saharan Africa.

Adaptive explanations have been offered for many physiological and morphological differences among human populations (Diamond 1992), although compelling empirical support is generally lacking. In recent years, some progress has been made by analyzing DNA sequence variation underlying phenotypes that distinguish human populations in different continental regions. For example, the incidence of infectious disease is known to vary among different geographic regions, and selection has probably played a significant role in shaping patterns of variation at disease-resistance genes in different human populations (Cavalli-Sforza, Menozzi, and Piazza 1994). Consistent with this idea, geographically localized selection for

disease resistance appears to have driven the frequency of the CCR5- Δ 32 allele to unusually high frequencies only in northern Europe (Stephens et al. 1998). Another physiological trait that is thought to have been subject to positive selection in populations outside of sub-Saharan Africa is lactase persistence (the persistence of intestinal lactase activity into adulthood; Bodmer and Cavalli-Sforza 1976). Consistent with this idea, positive selection appears to have driven a recently derived 'lactase-persistence' haplotype to high frequency only in northern Europe (Hollox et al. 2001). One of the most obvious phenotypic differences among human populations from different continental regions is skin pigmentation. Some form of natural and/or sexual selection is probably responsible for shaping global patterns of variation in human skin color, as differentiation in the level of skin pigmentation among continental populations vastly exceeds the level of differentiation observed at neutral genetic markers (Relethford 2002).

Although locus-specific surveys of DNA sequence variation can potentially elucidate the role of past selection in driving the differentiation of specific traits among human populations, individual case studies cannot provide an answer to the more general question of whether recent positive selection has been more prevalent in colonizing populations outside of sub-Saharan Africa. In principle, this hypothesis could be tested by conducting genomic scans of DNA variability in samples from different continental populations of humans. If recent positive selection has been more prevalent outside of Africa, multilocus neutrality tests based on DNA polymorphism or haplotype structure should identify a disproportionate number of candidate genes for selective sweeps in non-African populations. The underlying premise of multilocus neutrality tests is that demographic processes have relatively uniform effects across the entire genome, whereas the effects of selection are generally locus-specific and can be inferred from patterns of variation at linked sites (Cavalli-Sforza 1966; Lewontin and Krakauer 1973). For example, the spread and fixation of adaptive mutations results in the joint fixation of linked neutral variants ('genetic hitchhiking'; Maynard Smith and Haigh 1974). The strength of this hitchhiking effect is a function of the selection coefficient and recombinational distance from the

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Table 1
Data Sets Used for the Analysis of Microsatellite Variability in Samples from Each of Three Continents (Africa, Europe, and Asia)

| Data Set | D1 | D2 | D3 | D4 |
|-----------------------------|---|--|---|---|
| Number of loci | 95 | 92 | 60 | 377 |
| Repeat motif | Dinucleotide | Dinucleotide | Tetranucleotide | Di-, tri-, and tetranucleotide |
| African population samples | Biaka ($n = 132.27$) Mbuti ($n = 75.47$) | Biaka ($n = 34.35$) Mbuti ($n = 30.41$) | Biaka ($n = 9.03$) Mbuti ($n = 9.60$) San ($n = 27.38$) | Biaka ($n = 70.05$) Mbuti ($n = 28.93$) San ($n = 13.58$) |
| European population samples | Danish ($n = 111.44$) | N. Italian ($n = 40.37$) | French ($n = 37.07$) | French ($n = 55.89$) |
| Asian population samples | Han Chinese ($n = 93.48$) | Han Chinese ($n = 29.87$) | Han Chinese ($n = 33.08$) | Han Chinese ($n = 87.20$) |

NOTE.—For each continent, n = mean number of chromosomes sampled per locus.

selected site (Maynard Smith and Haigh 1974; Kaplan, Hudson, and Langley 1989; Stephan, Wiehe, and Lenz 1992; Wiehe and Stephan 1993). In general, genetic hitchhiking results in a reduced level of variability and a skewed distribution of allele frequencies at linked neutral loci (Tajima 1989; Fu and Li 1993; Braverman et al. 1995; Simonsen, Churchill, and Aquadro 1995).

In the case of geographically subdivided populations, hitchhiking with a locally adaptive mutation is expected to greatly increase the level of differentiation at linked neutral loci (Stephan and Mitchell 1992; Begun and Aquadro 1993; Stephan 1994; Stephan et al. 1998). Thus, loci that have undergone geographically restricted selective sweeps should be characterized by levels of differentiation that greatly exceed the genome-wide average.

Here we test the hypothesis that local adaptation in humans has been more prevalent in colonizing populations outside of sub-Saharan Africa. Using publicly available data, we conducted multilocus scans of microsatellite variability to identify regions of the human genome that may have been subject to continent-specific hitchhiking events. A previous genome scan of microsatellite variability in humans identified a number of candidate regions for divergent selection between African and European populations (Kayser, Brauer, and Stoneking 2003). Intriguingly, the authors reported an excess of loci that exhibited reduced variability in Europe relative to sub-Saharan Africa. Here we use a model-based approach to investigate this pattern in more detail using independent samples from European, Asian, and African populations and a much larger sample of marker loci. To the extent that our sample of marker loci is representative of the genome as a whole, results of the analysis provide further evidence that recent selective sweeps have been more prevalent in Europe and Asia than in sub-Saharan Africa.

Methods

Population Samples

We analyzed four microsatellite data sets that included polymorphism data for a total of 624 autosomal loci in multiple human populations (table 1). If we assume that hitchhiking effects typically extend 0.25–0.5 cM on either side of an adaptive mutation (e.g., Sabeti et al. 2002; Saunders, Hammer, and Nachman 2002), and that the sex-averaged length of the human genome is $\sim 3,615$ cM

(Kong et al. 2002), then our survey of 624 unlinked loci has effectively screened 4.3%–8.6% of the genome.

The first data set, D1 ($n=95$ dinucleotide repeat loci), is available online at <http://info.med.yale.edu/genetics/kkidd/abiinfo.html>. Data were available from a total of 102 loci. However, we excluded loci that were missing data from one or more of the African samples. The second data set, D2 ($n=92$ dinucleotide repeat loci), has been used in studies of demographic population structure (Bowcock et al. 1994; Jin et al. 2000), and these data are available online at www-evo.stanford.edu. The third data set, D3 ($n=60$ tetranucleotide repeat loci), has been used in studies of population structure (Jorde et al. 1995, 1997; Eller 1999) and these data were kindly provided by L. B. Jorde (University of Utah Health Sciences Center). The fourth data set, D4 ($n=377$ di-, tri-, and tetranucleotide repeat loci), has also been used in studies of population structure (Rosenberg et al. 2002; Zhivotovsky, Rosenberg, and Feldman 2003) and is available online at <http://research.marshfieldclinic.org/genetics/Freq/FreqInfo.htm>. For each of the four data sets, we used a single reference population to represent each of three continents: Africa, Asia, and Europe (table 1). For each comparison, we used a single, geographically restricted sample from each continent because using pooled allele counts from multiple, geographically dispersed localities could produce an artefactual skew in the distribution of allele frequencies within continents (Wakeley et al. 2001; Przeworski 2002; Ptak and Przeworski 2002; Hammer et al. 2003). This sampling problem would be especially severe within Africa because of the high degree of population subdivision (Yu et al. 2002). Because of the high degree of subdivision within Africa, and as a means of evaluating the consistency of locus-specific patterns of variation, we repeated all population comparisons using the Biaka and Mbuti as separate reference samples for Africa. The Biaka and Mbuti were the only African samples represented in the D1 and D2 data sets and they were the only samples that were common to all four data sets. For the D3 and D4 data sets, we also included the San as a third reference sample for Africa. We chose to use the San sample (rather than any of the other samples available in the D3 and D4 data sets) because previous studies have indicated that the San represent one of the most basal groups of modern humans (e.g., Chen et al. 2000; Ingman et al. 2000). Thus, inclusion of the San sample maximizes the coverage of African diversity in our analysis.

Three-way Population Comparisons

For each three-way population comparison, we obtained single-locus estimates of F_{ST} (a standardized measure of genetic differentiation) using the β statistic of Cockerham and Weir (1993):

$$\beta = \frac{F_0 - F_1}{1 - F_1}, \quad (1)$$

where $1 - F_1$ is the average probability of identity-by-descent for two alleles sampled randomly from separate subpopulations, and $1 - F_0$ is the average probability of identity-by-descent for two alleles sampled randomly from the same subpopulation. We estimated expected heterozygosity, H , as $1 - F_1$. For each data set, we tested for evidence of selection by comparing observed F_{ST} values (conditional on heterozygosity) to a null distribution generated by a coalescent-based simulation model.

Simulation results of Beaumont and Nichols (1996) indicate that conditional distributions of F_{ST} generated under an infinite island model are robust to a range of different nonequilibrium conditions. However, it is not clear whether this apparent robustness holds up in cases involving small numbers of demes. We therefore conducted coalescent simulations under a nonequilibrium model that incorporated population bottlenecks to account for founder effects associated with migrations out of Africa. Specifically, we extended the ‘multi-epoch’ model of Marth et al. (2004) to consider the case of three populations that diverged at a specified time in the past. Following the initial divergence (going forward in time), one of the populations remained stationary at the ancestral effective population size ($N_3 = 10,000$), whereas the other two populations each underwent an instant reduction in effective size ($N_2 = 1,000$). The duration of the population bottleneck was $T_2 = 550$ generations. The bottleneck was then followed by a stepwise increase of effective size to $N_1 = 10,000$, which occurred $T_1 = 3100$ generations before the present. For T_1 and T_2 , we used the average of maximum-likelihood parameter estimates obtained for Asian and European populations in the study of Marth et al. (2004). Similarly, we used a size expansion ratio ($N_1/N_2 = 10$) close to the average of maximum-likelihood parameter estimates obtained for these same samples under the ‘three-epoch’ model of Marth et al. (2004). To evaluate the effect of gene flow, we included a migration matrix that defined a three-deme island model. We conducted coalescent simulations under this nonequilibrium model of population structure to generate null distributions of F_{ST} over a range of migration rates.

Coalescent simulations were conducted under the stepwise mutation model (SMM). The mutation rate varied randomly over the range 1×10^{-5} to 5×10^{-4} (to generate a roughly uniform distribution of H values), and allele sizes were constrained to a range of 5 to 20 repeat units. In each set of iterations, sample sizes were set equal to the median of actual sample sizes in the specific data set under consideration. Coalescent simulations were used to generate a total of 50,000 paired values of F_{ST} and H , which was then used to compute the 0.95 and 0.50 quantiles of the conditional distribution (Beaumont and

Nichols 1996; Storz and Nachman 2003). We used F_{ST} as an estimator of differentiation rather than microsatellite-specific statistics such as R_{ST} because the former statistic is generally characterized by a lower sampling variance (Slatkin 1995; Gaggiotti et al. 1999; Balloux and Goudet 2002).

We used an iterative fitting procedure to generate the expected neutral distribution for each three-way population comparison. In each set of iterations, values for the migration matrix were varied over the range 1×10^{-5} to 5×10^{-4} to produce a null distribution in which equal numbers of loci fell above and below the median quantile. Loci with F_{ST} values that exceeded the 0.95 quantile of the resultant distribution were considered as preliminary candidates for continent-specific selective sweeps.

The set of candidate loci identified in each set of simulations may contain loci that are tracking selection at linked sites as well as loci that are false positives. All genome-wide scans for detecting selection face the problem of identifying and excluding false positives when multiple tests are conducted (e.g., Huttley et al. 1999; Akey et al. 2002; Payseur, Cutter, and Nachman 2002; Vigouroux et al. 2002; Luikart et al. 2003; Schlötterer 2003). To minimize this problem, we restricted further consideration to the subset of loci that appeared as outliers in separate comparisons using different reference populations for Africa (Biaka and Mbuti). For the D3 and D4 data sets, we also considered the smaller subset of loci that appeared as outliers in comparisons using all three different reference populations (Biaka, Mbuti, and San).

African Versus Non-African Comparisons

Although higher-than-expected F_{ST} values should be indicative of continent-specific selective sweeps, F_{ST} values alone cannot identify the populations in which the allele frequency changes took place. Thus, after identifying candidate loci that may have been subject to continent-specific sweeps, we then used pairwise comparisons to assess whether equal numbers of these loci exhibited reduced levels of relative variability in African and non-African populations. If recent selective sweeps have been more prevalent outside of Africa, then a disproportionate number of candidate loci should exhibit reduced levels of relative variability in non-African populations alone.

Under the SMM at mutation-drift equilibrium, expected heterozygosity (or ‘gene diversity,’ H ; Nei 1978) can be used to estimate the neutral parameter $\theta = 4N_e\mu$, where N_e = effective population size and μ = mutation rate (Ohta and Kimura 1973; Moran 1975). For two populations, the expected ratio of heterozygosity-based estimators of θ is:

$$E[RH] = \frac{\left(\left(\frac{1}{1-H_{\text{pop1}}}\right)^2 - 1\right) \frac{1}{8\mu}}{\left(\left(\frac{1}{1-H_{\text{pop2}}}\right)^2 - 1\right) \frac{1}{8\mu}} \approx \frac{\left(\frac{1}{1-H_{\text{pop1}}}\right)^2 - 1}{\left(\frac{1}{1-H_{\text{pop2}}}\right)^2 - 1}. \quad (2)$$

For each locus we used estimates of African gene diversity in the numerator of the ratio and the arithmetic average of European and Asian gene diversities in the denominator,

Table 2
Genetic Differentiation Among African, European, and Asian Population Samples

| Data Set | Populations | Weighted Mean F_{ST} | Median No. Chromosomes/ Sample |
|----------------------|------------------------------|------------------------|-----------------------------------|
| D1 ($n = 95$ loci) | Biaka-Danish-Han Chinese | 0.112 | 111 |
| | Mbuti-Danish-Han Chinese | 0.124 | 92 |
| D2 ($n = 92$ loci) | Biaka-N. Italian-Han Chinese | 0.122 | 23 |
| | Mbuti-N. Italian-Han Chinese | 0.134 | 23 |
| D3 ($n = 60$ loci) | Biaka-French-Han Chinese | 0.151 | 26 |
| | Mbuti-French-Han Chinese | 0.164 | 26 |
| | San-French-Han Chinese | 0.122 | 33 |
| D4 ($n = 377$ loci) | Biaka-French-Han Chinese | 0.137 | 70 |
| | Mbuti-French-Han Chinese | 0.157 | 57 |
| | San-French-Han Chinese | 0.166 | 52 |

following Schlötterer (2002). We considered Europe and Asia jointly because we are specifically interested in testing the hypothesis that selective sweeps have been more prevalent outside of sub-Saharan Africa. If the majority of higher-than-expected F_{ST} values are attributable to selective sweeps outside of Africa, then a disproportionate number of candidate loci should have RH values that fall above the median of the genome-wide distribution in each pairwise comparison between African and non-African populations. Since the estimate of African gene diversity is in the numerator of the ratio, RH values that fall above the median of the distribution indicate a reduced level of relative variability in non-African populations. Loci that show only a modest difference in gene diversity between populations (and which therefore fall just slightly above or below the median value) are more likely to be false-positives than loci that show a more pronounced discrepancy in relative levels of gene diversity (and which therefore show a higher deviation from the genome-wide average). To maximize the probability of excluding false positives from the African versus non-African comparisons, we only considered loci with \ln -transformed RH values that fell above or below 0.5 standard deviations (SDs) of the genome-wide average. In cases where loci were monomorphic in one population, we substituted an H value of 0.0001 for zero.

By considering ratios of θ values, we are able to control for interlocus differences in levels of variability that are attributable to differences in mutation rate and/or recombinational environment. For the ratios of θ values, we used estimators based on gene diversity ($\ln RH$) rather than variance in allele size ($\ln RV$; Schlötterer 2002), because $\ln RH$ is characterized by a much lower variance and is less sensitive to departures from the SMM (Kauer, Dieringer, and Schlötterer 2003).

Results

Three-way Population Comparisons

Mean F_{ST} estimates for the three-way population comparisons ranged from 0.1117 to 0.1661 (table 2). In the four comparisons using Biaka as the reference sample for Africa, a total of 26 loci were identified as candidates for selection (one locus from the D1 data set, six from D2, four from D3, and 15 from D4; fig 1). In the comparisons

using Mbuti as the reference sample for Africa, a total of 25 loci were identified as candidates for selection (four loci from the D1 data set, four from D2, five from D3, and 12 from D4; fig. 2). In the separate comparisons using Biaka and Mbuti samples, 18 of the same loci were identified as candidates for selection. In the two comparisons using San as the reference sample for Africa, a total of 16 loci were identified as candidates for selection (three loci from the D3 data set and 13 from D4; fig. 3). In the three separate comparisons using Biaka, Mbuti, and San samples (D3 and D4 data sets only), seven of the same loci were identified as candidates for selection.

African Versus Non-African Comparisons

Consistent with the results of previous surveys of DNA variability in humans (reviewed by Harpending and Rogers 2000), average levels of gene diversity tended to be slightly higher in African than in non-African populations (table 3). The exceptions to this general pattern can probably be attributed to the fact that the Biaka, Mbuti, and San samples represent restricted subsets of African diversity.

Of the 18 loci identified as candidates for selection in the separate three-way comparisons using Biaka and Mbuti samples, 13 loci exhibited differences in relative levels of variability between African and non-African populations (i.e., $\ln RH$ values fell more than 0.5 SDs from the means of both distributions). If recent selective sweeps have occurred with equal frequency inside and outside of Africa, then roughly equal numbers of candidate loci should exhibit reduced levels of relative variability in African and non-African populations. We can reject this null hypothesis, as only one locus exhibited a reduced level of relative variability in Africa and 12 loci exhibited reduced levels of relative variability outside of Africa ($\chi^2_1 = 9.31$, $P = 0.0055$; table 4). Of the seven loci identified as candidates for selection in the separate comparisons using Biaka, Mbuti, and San samples (D3 and D4 data sets only), five loci exhibited discrepancies in relative levels of variability between African and non-African populations (using the same 0.5 SD cut-off for all three distributions). All five loci exhibited reduced levels of relative variability outside of Africa. The result for this smaller subset of loci further bolsters the conclusion that a disproportionate

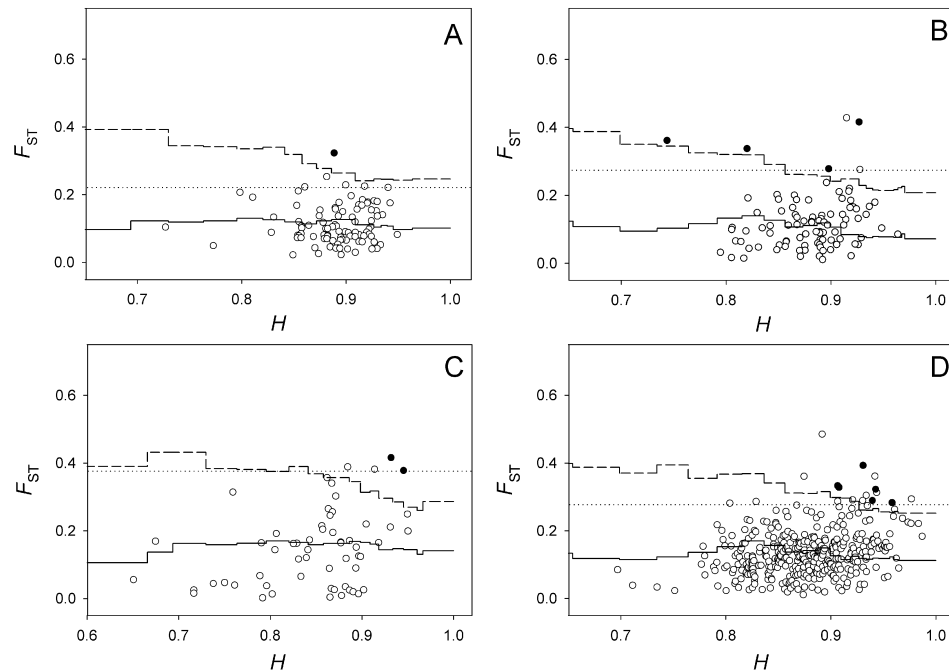


FIG. 1.—Results of three-way population comparisons using the Biaka as a reference sample for Africa. Estimated F_{ST} values for microsatellite loci are plotted as a function of heterozygosity. The 0.95 and 0.50 quantiles of the simulation-based distribution are denoted by dashed and solid lines, respectively. The horizontal dotted line denotes the 0.95 quantile of the empirical distribution of F_{ST} . Filled symbols denote candidate loci for geographically restricted selective sweeps (based on criteria described in the text). (A) Results for the D1 data set ($n = 95$ loci); (B) results for the D2 data set ($n = 92$ loci); (C) results for the D3 data set ($n = 60$ loci); (D) results for the D4 data set ($n = 377$ loci).

number of candidate loci exhibit reduced variability outside of Africa.

Loci that were identified as outliers in the model-based analysis were also characterized by extreme values

in the empirical distribution of F_{ST} for each three-way population comparison (table 5). Of the 13 loci identified as candidates for selection in the comparisons using the Biaka and Mbuti samples (table 4), 11 were characterized

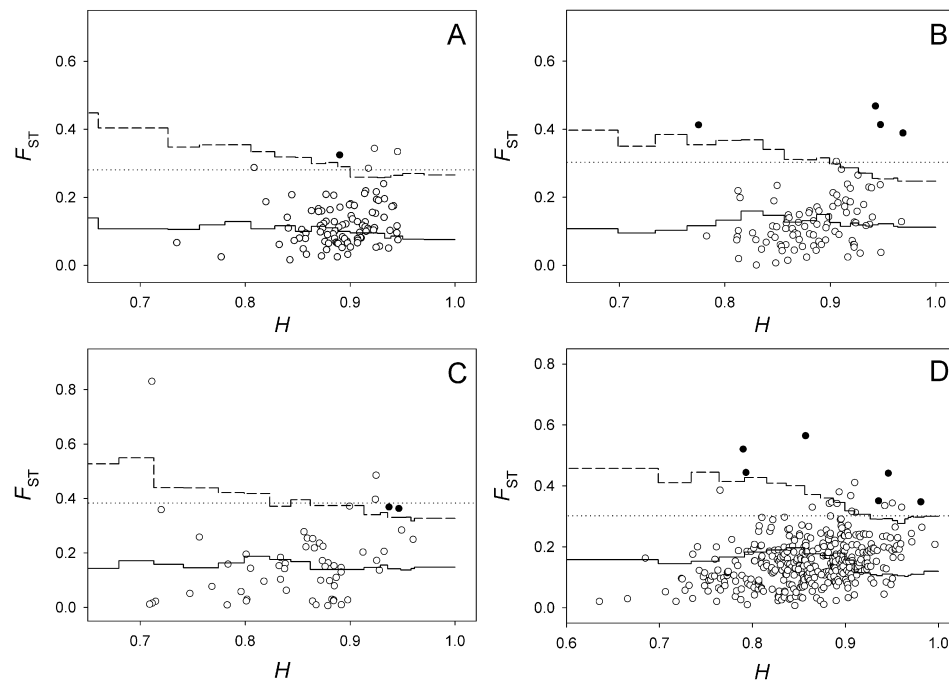


FIG. 2.—Results of three-way population comparisons using the Mbuti as a reference sample for Africa. Estimated F_{ST} values for microsatellite loci are plotted as a function of heterozygosity. The 0.95 and 0.50 quantiles of the simulation-based distribution are denoted by dashed and solid lines, respectively. The horizontal dotted line denotes the 0.95 quantile of the empirical distribution of F_{ST} . Filled symbols denote candidate loci for geographically restricted selective sweeps (based on criteria described in the text). (A) Results for the D1 data set ($n = 95$ loci); (B) results for the D2 data set ($n = 92$ loci); (C) results for the D3 data set ($n = 60$ loci); (D) results for the D4 data set ($n = 377$ loci).

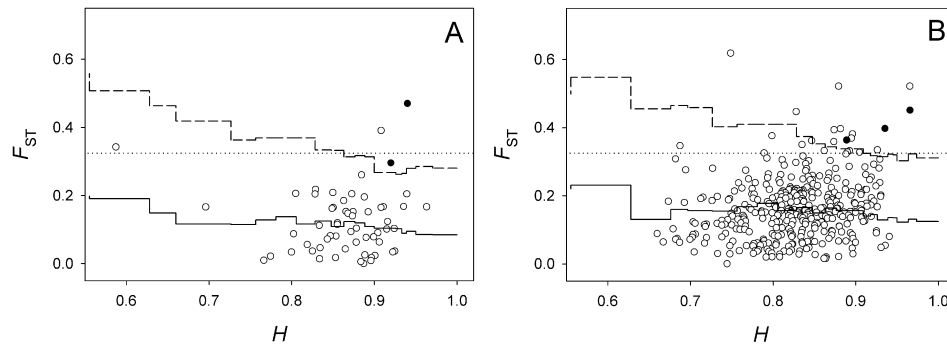


FIG. 3.—Results of three-way population comparisons using the San as a reference sample for Africa. Estimated F_{ST} values for microsatellite loci are plotted as a function of heterozygosity. The 0.95 and 0.50 quantiles of the simulation-based distribution are denoted by dashed and solid lines, respectively. The horizontal dotted line denotes the 0.95 quantile of the empirical distribution of F_{ST} . Filled symbols denote candidate loci for geographically restricted selective sweeps (based on criteria described in the text). (A) Results for the D3 data set ($n = 60$ loci); (B) results for the D4 data set ($n = 377$ loci).

by F_{ST} values that fell in the upper 0.05 tails of both empirical distributions, and all 13 fell in the upper 0.10 tails (table 5). Of the five loci identified as candidates for selection in the separate comparisons using the Biaka, Mbuti, and San samples (D3 and D4 data sets only), three were characterized by F_{ST} values that fell in the upper 0.05 tails of each of the three empirical distributions, and all five fell in the upper 0.10 tails (table 5).

Discussion

We analyzed genome-wide patterns of DNA polymorphism to test the hypothesis that local adaptation in humans has been more prevalent in colonizing populations outside of sub-Saharan Africa. We conducted a genome scan of microsatellite variability within and among the three major continental populations of humans and identified a number of candidate loci for geographically restricted hitchhiking events. A disproportionate number of these loci exhibited reduced levels of relative variability

in non-African populations alone. This result is consistent with the hypothesis that recent positive selection has been more prevalent outside of sub-Saharan Africa. This result is also consistent with the results of another recent study (Kayser, Brauer, and Stoneking 2003) that identified a larger number of candidate loci for positive selection in non-African populations than in African populations. None of our 13 candidate loci identified the same genomic regions as those identified by Kayser, Brauer, and Stoneking (2003), as locations of candidate loci on the same chromosome were never closer than 20 cM. This lack of correspondence is not too surprising given the relatively low combined marker density of the two studies.

Of the 11 outlier loci identified as candidates for selection by Kayser, Brauer, and Stoneking (2003), five were also included in the D4 data set that we analyzed. Although these five loci were characterized by unusually large R_{ST} values between African and European population samples in the study of Kayser, Brauer, and Stoneking (2003), none of them were identified as outliers in our

Table 3
Summary Statistics for Microsatellite Variability Within Population Samples from Three Continents, from Each of Four Independent Data Sets

| Data Set | Population | N_A | H | V | Skewness | Kurtosis |
|----------------------|-------------|-------|-------|--------|----------|----------|
| D1 ($n = 95$ loci) | Biaka | 10.37 | 0.807 | 9.661 | 0.087 | 3.330 |
| | Mbuti | 8.91 | 0.783 | 7.265 | 0.106 | 3.350 |
| | Danish | 9.50 | 0.777 | 7.512 | -0.104 | 3.172 |
| | Han Chinese | 8.43 | 0.711 | 6.805 | -0.073 | 3.730 |
| D2 ($n = 92$ loci) | Biaka | 6.53 | 0.763 | 7.441 | 0.077 | 2.554 |
| | Mbuti | 5.24 | 0.682 | 7.969 | -0.059 | 2.659 |
| | N. Italian | 6.53 | 0.736 | 7.955 | -0.047 | 2.885 |
| | Han Chinese | 6.11 | 0.746 | 8.743 | 0.077 | 2.606 |
| D3 ($n = 60$ loci) | Biaka | 4.42 | 0.672 | 5.093 | -0.074 | 1.975 |
| | Mbuti | 4.57 | 0.663 | 5.321 | 0.056 | 2.176 |
| | San | 6.57 | 0.728 | 3.963 | -0.192 | 2.942 |
| | French | 6.40 | 0.713 | 4.305 | -0.079 | 3.017 |
| | Han Chinese | 6.02 | 0.671 | 5.124 | 0.079 | 3.300 |
| D4 ($n = 377$ loci) | Biaka | 7.72 | 0.762 | 13.032 | -0.099 | 2.950 |
| | Mbuti | 6.55 | 0.743 | 12.816 | -0.015 | 2.817 |
| | San | 5.08 | 0.704 | 12.470 | -0.016 | 2.400 |
| | French | 6.89 | 0.739 | 10.996 | -0.080 | 2.893 |
| | Han Chinese | 7.14 | 0.717 | 10.165 | 0.064 | 3.259 |

NOTE.— N_A , number of alleles; H , expected heterozygosity; V , variance in allele size.

Table 4
Loci Identified as Outliers in the Three-way Population Comparisons that Also Exhibited a Discrepancy in Relative Levels of Variability Between African and Non-African Populations

| Locus | Chromosome | Map Position (Marshfield map; Broman et al. 1998) | Local Recombination Rate (cM/Mb) | Continental Population Showing Reduced Variability | No. of Genes Within a 0.5 cM Window Centered on the Marker Locus | Identity of Known Genes Within the 0.5 cM Window |
|----------|------------|---|--|--|---|--|
| D3S4523 | 3 | 138.00 cM | 0.8 | non-African | 56 | IGSF11, FLJ32859, UPK1B, B4GALT4, CDGAP, FLJ10902, MDS010, C3orf1, CD80, CSRP2P, ADPRH, PLA1A, POPDC2, COX17, AAT-1, NR112, GSK3B, GPR156, FSTL1, NDUFB4, HGD, RABL3, GTF2E1, KIAA1006, POLQ, HCLS1, GOLGB1, KIAA0036, EAF2, SLC15A2, MGC50831, CD86, CASR, CSTA, E2IG5, WDR5B, KPNA1, BAL, BBAP, FLJ40597, KIAA1268, HSPBAP1 |
| D3S2418 | 3 | 215.84 cM | 2.0 | non-African | 2 | FGF12 |
| D4S3360 | 4 | 0.0 cM | 1.3 | African | 2 | FLJ90036 |
| D6S400 | 6 | 63.28 cM | 1.7 | non-African | 14 | TFEB, PGC, FRS3, C6orf49, MGC20741, USP49, BYSL, CCND3, TBN, GUCA1A, GUCA1B, MRPS10, TRERF |
| D10S597 | 10 | 128.73 cM | 0.5 | non-African | 8 | XPNPEP1, RNU4P5, ADD3, MXI1, SMNDC1 |
| D10S212 | 10 | 170.94 cM | 2.2 | non-African | 31 | BNIP3, C10orf39, DPYSL4, PKE, KIAA1674, INPP5A, NKX6-2, DKFZp434A1721, FLJ25954, GPR123, KIAA1768, RASGEF2, UTF1, VENTX2, ADAM8, TUBGCP2, CALCYON, UPA, FLJ26016, ECHS1, PAOX, Sprn, OR6L1P |
| D15S165 | 15 | 20.24 cM | 1.0 | non-African | 23 | DKFZP434L187, CHRFBAM7A, KIAA1018, FLJ20313, TRPM1 |
| D15S148 | 15 | 52.33 cM | 3.2 | non-African | 18 | LIPC, ADAM10, KIAA1164, FLJ13213, RNF111, CCNB2, MYO1E, LDHL, MGC26690, GCNT3, GTF2A2, BNIP2, RPS3A-like, FOXB1 |
| D16S508 | 16 | 57.79 | 0.6 | non-African | 50 | XP06, LAT1-3TM, MVP, PSK-1, PSK, ITGAL, ITGAM, ZNF267, TP53TG3, SHCBP1, GPT2, NETO2, CDA08, PHKB, ABCC12, ABCC11, LONP, N4BP1, OAZ, FLJ20718, BRD7, NKD1, CYLD, TNRC9, FLJ12178, RBL2, KIAA1005, FTO, FLJ20481, SLC6A2, GNAO1, AMFR, KIAA0095, SLC6A3, NOD27, CPNE2, KIAA1972, TM4SF11, GPR56, DKFZp434I099, KIFC3, CNGB1, CSNK2A2, NDRG4, KIAA1007, CDH8 |
| D17S2180 | 17 | 66.85 cM | 0.8 | non-African | 60 | NSF, WNT3, WNT9B, GOSR2, CDC27, MYL4, ITGB3, FLJ40342, NPEPPS, KPNB1, ProSAPIP2, TBX21, OSBPL7, MRPL10, MGC16309, SCRIN2, SP6, SP2, PNPO, MGC11242, CDK5RAP3, COPZ2, NFE2L1, CBX1, SNX11, SCAP1, HOXB1, HOXB2, HOXB3, HOXB4, HOXB5, HOXB6, HOXB7, HOXB8, HOXB9, PRAC, HOXB13, FLJ35808, NDP52, ATP5G1, FLJ13855, EAP30, GIP, IMP-1, GALGT2, GNGT2, NESH, PHOSPHO1, KIAA0924, PHB, NGFR |

Table 4
Continued

| Locus | Chromosome | Map Position (Marshfield map; Broman et al. 1998) | Local Recombination Rate (cM/Mb) | Continental Population Showing Reduced Variability | No. of Genes Within a 0.5 cM Window Centered on the Marker Locus | Identity of Known Genes Within the 0.5 cM Window |
|----------|------------|---|--|--|---|--|
| D19S403 | 19 | 32.94 cM | 1.8 | non-African | 27 | ZNF177, ZNF266, ZNF560, ZNF426, ZNF561, ZNF562, MGC45408, FLJ20079, UBE2L4, FBXL12, PIN1, OLFM2, COL5A3, RDH8, FLJ11286, ANGPTL-6, PPN, P2RY11, EIF3S4, DNMT1 |
| D20S103 | 20 | 2.13 cM | 5.2 | non-African | 2 | CSNK2A1, TCF15 |
| UTSW1523 | unknown | unknown | | non-African | | |

F_{ST} -based simulation analyses. Since Kayser, Brauer, and Stoneking (2003) used different population samples for Europe and sub-Saharan Africa, a lack of correspondence between the results of our studies would be expected if selection was geographically restricted to specific sub-populations within continents. However, a replicated test using different population samples should identify loci that were subject to continent-wide selective sweeps. To assess whether these five loci also exhibit unusually high levels of differentiation in the D4 data set, we estimated locus-

specific F_{ST} and R_{ST} values for each of the six possible pairwise comparisons between our African and non-African population samples. Two of the five loci (D9S2169 and D2S1400) fell in the upper 0.05 tail of the empirical distribution of R_{ST} values in each of the six pairwise comparisons (table 6). The D2S1400 locus also exhibited the highest F_{ST} value in the pairwise comparison between the San and Han Chinese samples, but neither D9S2169 nor any of the other three loci fell in the upper tails of the empirical distributions of F_{ST} . Rank

Table 5
Levels of Differentiation at Candidate Loci for Geographically Restricted Sweeps

| Data set | Locus | Three-way Comparison | F_{ST} | Ranking (%) |
|----------|----------|------------------------------|----------|-------------------|
| D1 | D10S597 | Biaka-Danish-Han Chinese | 0.323 | 1 of 95 (0.01) |
| | | Mbuti-Danish-Han Chinese | 0.325 | 3 of 95 (0.03) |
| D2 | D15S148 | Biaka-N. Italian-Han Chinese | 0.416 | 2 of 92 (0.02) |
| | | Mbuti-N. Italian-Han Chinese | 0.414 | 2 of 92 (0.02) |
| | D15S165 | Biaka-N. Italian-Han Chinese | 0.278 | 5 of 92 (0.05) |
| | | Mbuti-N. Italian-Han Chinese | 0.389 | 4 of 92 (0.04) |
| | D16S508 | Biaka-N. Italian-Han Chinese | 0.361 | 3 of 92 (0.03) |
| | | Mbuti-N. Italian-Han Chinese | 0.413 | 3 of 92 (0.03) |
| | UTSW1523 | Biaka-N. Italian-Han Chinese | 0.337 | 4 of 92 (0.04) |
| | | Mbuti-N. Italian-Han Chinese | 0.468 | 1 of 92 (0.01) |
| D3 | D19S403 | Biaka-French-Han Chinese | 0.378 | 4 of 60 (0.07) |
| | | Mbuti-French-Han Chinese | 0.363 | 6 of 60 (0.10) |
| | | San-French-Han Chinese | 0.470 | 1 of 60 (0.02) |
| | D6S400 | Biaka-French-Han Chinese | 0.416 | 1 of 60 (0.02) |
| | | Mbuti-French-Han Chinese | 0.369 | 5 of 60 (0.08) |
| | | San-French-Han Chinese | 0.296 | 4 of 60 (0.07) |
| D4 | D4S3360 | Biaka-French-Han Chinese | 0.322 | 8 of 377 (0.02) |
| | | Mbuti-French-Han Chinese | 0.344 | 12 of 377 (0.03) |
| | | San-French-Han Chinese | 0.224 | 76 of 377 (0.20) |
| | D10S212 | Biaka-French-Han Chinese | 0.393 | 2 of 377 (0.01) |
| | | Mbuti-French-Han Chinese | 0.368 | 8 of 377 (0.02) |
| | | San-French-Han Chinese | 0.362 | 13 of 377 (0.03) |
| | D3S2418 | Biaka-French-Han Chinese | 0.283 | 17 of 377 (0.05) |
| | | Mbuti-French-Han Chinese | 0.330 | 17 of 377 (0.05) |
| | | San-French-Han Chinese | 0.451 | 4 of 377 (0.01) |
| | D20S103 | Biaka-French-Han Chinese | 0.289 | 14 of 377 (0.04) |
| | | Mbuti-French-Han Chinese | 0.335 | 15 of 377 (0.04) |
| | | San-French-Han Chinese | 0.397 | 6 of 377 (0.02) |
| | D3S4523 | Biaka-French-Han Chinese | 0.333 | 6 of 377 (0.02) |
| | | Mbuti-French-Han Chinese | 0.411 | 5 of 377 (0.01) |
| | | San-French-Han Chinese | 0.118 | 259 of 377 (0.69) |
| | D17S2180 | Biaka-French-Han Chinese | 0.328 | 7 of 377 (0.02) |
| | | Mbuti-French-Han Chinese | 0.380 | 7 of 377 (0.02) |
| | | San-French-Han Chinese | 0.364 | 12 of 377 (0.03) |

NOTE.—The ranking of locus-specific F_{ST} values (in descending order) and their associated percentiles are specific to each of the four data sets.

Table 6
Levels of Differentiation at Five Loci that Were Identified as Outliers by Kayser, Brauer, and Stoneking (2003)

| Locus | Biaka-French | | Biaka-Han Chinese | | Mbuti-French | | Mbuti-Han Chinese | | San-French | | San-Han Chinese | |
|---|------------------------|------------------------------|------------------------|------------------------------|------------------------|------------------------------|------------------------|------------------------------|------------------------|-----------------------------|-----------------------------|-----------------------------|
| | F_{ST} | R_{ST} | F_{ST} | R_{ST} | F_{ST} | R_{ST} | F_{ST} | R_{ST} | F_{ST} | R_{ST} | F_{ST} | R_{ST} |
| D16S539 | 0.116 149 (0.40) | 0.070 101 (0.27) | 0.081 244 (0.65) | -0.005 302 (0.80) | 0.038 304 (0.81) | 0.177 49 (0.13) | 0.032 333 (0.88) | 0.023 183 (0.49) | 0.300 32 (0.08) | 0.036 145 (0.39) | 0.225 106 (0.28) | -0.010 354 (0.94) |
| D21S1437 | 0.117 142 (0.38) | 0.129 51 (0.14) | 0.264 31 (0.08) | 0.006 252 (0.67) | 0.124 149 (0.40) | 0.068 116 (0.31) | 0.350 28 (0.07) | -0.001 363 (0.96) | 0.119 161 (0.43) | 0.224 26 (0.07) | 0.385 32 (0.08) | 0.073 104 (0.28) |
| D9S2169 | 0.103 166 (0.44) | 0.256 10 (0.03) | 0.064 277 (0.73) | 0.287 15 (0.04) | 0.084 221 (0.59) | 0.331 11 (0.03) | 0.059 277 (0.73) | 0.342 13 (0.03) | 0.078 235 (0.62) | 0.351 6 (0.02) | 0.134 179 (0.47) | 0.351 6 (0.02) |
| D2S1400 | 0.085 204 (0.54) | 0.293 7 (0.02) | 0.043 320 (0.85) | 0.410 5 (0.01) | 0.066 259 (0.69) | 0.477 3 (0.01) | 0.014 357 (0.95) | 0.560 3 (0.01) | 0.294 40 (0.11) | 0.345 7 (0.02) | 0.704 1 (0.00) | 0.431 3 (0.01) |
| D6S1031 | 0.170 68 (0.18) | 0.253 11 (0.03) | 0.228 46 (0.12) | 0.087 91 (0.24) | 0.140 134 (0.04) | 0.090 99 (0.26) | 0.184 128 (0.34) | -0.001 316 (0.84) | 0.098 197 (0.52) | 0.328 8 (0.02) | 0.138 176 (0.47) | 0.065 111 (0.29) |
| Average ($n = 5$) | 0.118 | 0.200 | 0.136 | 0.157 | 0.090 | 0.229 | 0.128 | 0.185 | 0.178 | 0.257 | 0.317 | 0.182 |
| Genome-wide average ($n = 377$) | 0.111 | 0.066 | 0.129 | 0.068 | 0.125 | 0.075 | 0.163 | 0.069 | 0.138 | 0.054 | 0.175 | 0.048 |

NOTE.—Locus-specific F_{ST} and R_{ST} values and their rank order in the empirical distributions are given for each of six pairwise comparisons between African and non-African populations. The ranking of locus-specific F_{ST} and R_{ST} values (in descending order) and their associated percentiles are specific to the D4 data set ($n = 377$ loci). Values that fell in the upper 0.05 tail of the empirical distributions are in bold.

correlations between single-locus F_{ST} and R_{ST} values were not statistically significant in any of the six pairwise comparisons (Spearman's rank correlation coefficient ranged from 0.077 to 0.024). In summary, two of the outliers identified by Kayser, Brauer, and Stoneking (2003) also appear as outliers in our analysis using completely independent population samples. However, patterns of variation at these loci are only unusual with respect to variance in allele size, not heterozygosity.

Aside from the generally lower sampling variance of F_{ST} relative to R_{ST} (Slatkin 1995; Gaggiotti et al. 1999; Balloux and Goudet 2002), statistics based on different measures of polymorphism may be sensitive to the effects of selection over different time scales. Since heterozygosity is expected to return to its equilibrium value more rapidly than variance in allele size following a population bottleneck or selective sweep (Kimmel et al. 1998), test statistics based on allele identity may have more power to detect sweeps that have occurred during a relatively recent time interval, whereas test statistics based on allele size may have more power to detect sweeps that occurred in the more distant past. If this is the case, then candidate loci identified by Kayser, Brauer, and Stoneking (2003) may be implicated in more ancient selective sweeps than the candidate loci that we have identified. In any case, the two loci that appeared as outliers in the empirical distributions of R_{ST} both show severely reduced levels of variability in non-African populations relative to Africa, consistent with the pattern exhibited by the candidate loci identified by our F_{ST} -based tests.

The nonequilibrium demographic model that we used was highly conservative with regard to the identification of outliers. Simulations under an equilibrium island model of

population structure typically predicted a sharper decline in F_{ST} at high values of H , consistent with the results of Flint et al. (1999). Consequently, greater numbers of loci exceeded the upper quantile of the distribution null at H values above ~ 0.90 . However, the same 13 loci listed in table 4 were consistent outliers in simulations that covered a wide range of different equilibrium and nonequilibrium models of population structure (data not shown).

Because African and non-African populations have experienced different demographic histories, it is reasonable to expect them to be characterized by different standing levels of DNA variability and different distributions of allele frequencies. However, the use of multilocus data allows us to distinguish between the locus-specific effects of selection and the genome-wide effects of demographic processes. Moreover, by considering the distribution of gene-diversity ratios in the pairwise population comparisons, we are able to control for differences in absolute levels of variability between continents.

The microsatellite loci listed in table 4 are flanked by 2–60 genes within a 0.25 cM window on either side. One or more loci within these chromosomal regions may be expected to harbor adaptive mutations that have been driven to unusually high frequencies within a single continental region. This list of candidate genes can be considered as a starting point for efforts to characterize functional polymorphisms that underlie adaptive differentiation in the human gene pool. Using estimates of local recombination rates taken from Kong et al. (2002), we assessed whether candidate loci were disproportionately represented in genomic regions of low recombination. We found this not to be the case, as only five candidate loci

were characterized by local recombination rates that fell below the genome-wide average of 1.1 cM/Mb (Kong et al. 2002). Thus, if the candidate loci are in fact tracking selection at linked sites, they may be tightly linked to the targets of selection.

Using Genome Scans to Infer Selective Sweeps

The results presented here will be a valuable complement to data from genome-wide surveys of nucleotide polymorphism once such data become more widely available. Comparing multilocus patterns of nucleotide and microsatellite polymorphism can be expected to provide many novel insights into the evolutionary processes that shape patterns of genomic diversity. For example, following a selective sweep, single nucleotide polymorphism and microsatellite length polymorphism will exhibit very different rates of return to mutation-drift equilibrium because mutation rates differ by several orders of magnitude. Deterministic and stochastic models of hitchhiking at microsatellite loci have demonstrated that the strength of hitchhiking effects depends strongly on mutation rates in addition to recombination rates and the selection coefficient (Wiehe 1998). Thus, comparing patterns of nucleotide and microsatellite polymorphism can be expected to provide valuable information about the timing of hitchhiking events. Given the high mutation rates at human microsatellite loci (3×10^{-3} to 6×10^{-4} ; Ellegren 2000), theoretical results of Wiehe (1998) suggest that surveys of microsatellite variation are most appropriate for detecting selective sweeps that were both strong and recent (e.g., during the Neolithic). This stands in contrast to nucleotide variation, which may be more appropriate for detecting relatively ancient sweeps, as mutation rates for single nucleotide changes are generally at least four orders of magnitude lower ($\sim 2 \times 10^{-8}$; Nachman and Crowell 2000a). In addition, microsatellites may generally provide more power than single nucleotide changes for detecting sweeps, because reductions in microsatellite variability will occur relative to a much higher baseline level of standing variation.

Recent studies of both humans and *Drosophila* have revealed substantial differences in patterns of DNA variability between African and non-African populations (Begun and Aquadro 1993; Andolfatto 2001; Harr, Kauer, and Schlötterer 2002; Kauer et al. 2002; Glinka et al. 2003; Kauer, Dieringer, and Schlötterer 2003). These differences may largely reflect founder effects associated with migrations out of Africa. However, patterns of DNA variability may also reflect the effects of positive selection associated with the colonization of novel environments outside the ancestral species range. Consistent with this hypothesis, patterns of nucleotide and microsatellite variability in African and non-African populations of *D. melanogaster* have been interpreted as evidence for geographically restricted selective sweeps associated with adaptation to temperate zone environments (Andolfatto 2001; Harr, Kauer, and Schlötterer 2002; Kauer et al. 2002; Glinka et al. 2003; Kauer, Dieringer, and Schlötterer 2003). Although several studies have documented directional selection on loci involved in disease resistance

within African populations of humans (Hamblin and Di Rienzo 2000; Tishkoff et al. 2001; Hamblin, Thompson, and Di Rienzo 2002; Sabeti et al. 2002; Saunders, Hammer, and Nachman 2002), in each case there were a priori reasons to expect that the genes under consideration were involved in local adaptation. By contrast, geographic surveys of X-linked loci in humans that were not previously implicated as candidates for local adaptation have revealed evidence of genetic hitchhiking events that appear to have been largely restricted to non-African populations (e.g., Harris and Hey 1999, 2001; Nachman and Crowell 2000b). Our finding that selective sweeps may have been more prevalent outside of Africa appears to be consistent with the picture emerging from global surveys of DNA sequence variation in humans. It remains to be seen whether surveys of X-linked loci will reveal additional evidence for selective sweeps outside of Africa, as in the case of *Drosophila* (Andolfatto 2001; Harr, Kauer, and Schlötterer 2002; Kauer et al. 2002; Glinka et al. 2003; Kauer, Dieringer, and Schlötterer 2003).

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