# African human diversity, origins and migrations

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The continent of Africa is thought to be the site of origin of all modern humans and is the more recent origin of millions of African Americans. Although Africa has the highest levels of human genetic diversity both within and between populations, it is under-represented in studies of human genetics. Recent advances have been made in understanding the origins of modern humans within Africa, the rate of adaptations due to positive selection, the routes taken in the first migrations of modern humans out of Africa, and the degree of admixture with archaic populations. Africa is also in dire need of effective medical interventions, and studies of genetic variation in Africans will shed light on the genetic basis of diseases and resistance to infectious diseases. Thus, we have tremendous potential to learn about human variation and evolutionary history and to positively impact human health care from studies of genetic diversity in Africa.

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**Current Opinion in Genetics & Development** 2006, **16**:597–605

This review comes from a themed issue on
Genomes and evolution
Edited by Chris Tyler-Smith and Molly Przeworski

Available online 23th October 2006

0959-437X/$ – see front matter


**DOI** 10.1016/j.gde.2006.10.008

## Introduction

Africa contains a considerable amount of diversity, not only in regard to genetic diversity but also in regard to cultural, linguistic and phenotypic diversity [1]. The continent of Africa has been estimated to contain over 2000 distinct ethno-linguistic groups — speaking languages that constitute nearly a third of the worlds living languages (http://www.ethnologue.com/). Primary subsistence patterns within Africa include various modes of agriculture, pastoralism and some of the last remnants of the world's hunter-gatherers. Africans live in climates that range from those of the world's largest desert and second largest tropical rainforest to those of savanna, swamps and mountain highlands, and these climates have, in some cases, undergone dramatic shifts in the past 10 000 years [2]. In addition to high levels of genetic variation within populations, Africa also has high levels of genetic divergence between populations (reviewed in [1,3]). Patterns of genetic variation in Africa have been influenced by several short-range, in addition to long-range, migration events (e.g. the migration of agricultural Bantu-speakers from West Africa throughout Sub-Saharan Africa within the past 4000 years; summarized in [1,3]). Africa is the more recent site of origin of millions of African Americans, many of whom are now turning to genetic studies to infer their ancestry. The continent of Africa also has an extremely high mortality rate from infectious disease, with malaria and HIV alone responsible for millions of deaths per year (http://www.cdc.gov/malaria/index.htm) [4]. Studies of genetic variation in Africans and African descendants in the Americas might shed light on the genetic basis of resistance to these infectious diseases, as well as revealing more about the role of pharmacogenetic variation on effectiveness of drugs used to treat them. Thus, the richness of Africa for human genetic, anthropological and medical studies is unparalleled.

Here, we review some recent advances in understanding the demographic and selective history of our species in Africa, with particular attention paid to the possible role of inversion polymorphisms and how this might confound recent inferences. We also discuss the recent interest and limitations in using genetic studies to infer personal ancestries and examine the potential impact that studies in Africa can have on medical intervention and understanding the genetic basis of infectious and complex diseases.

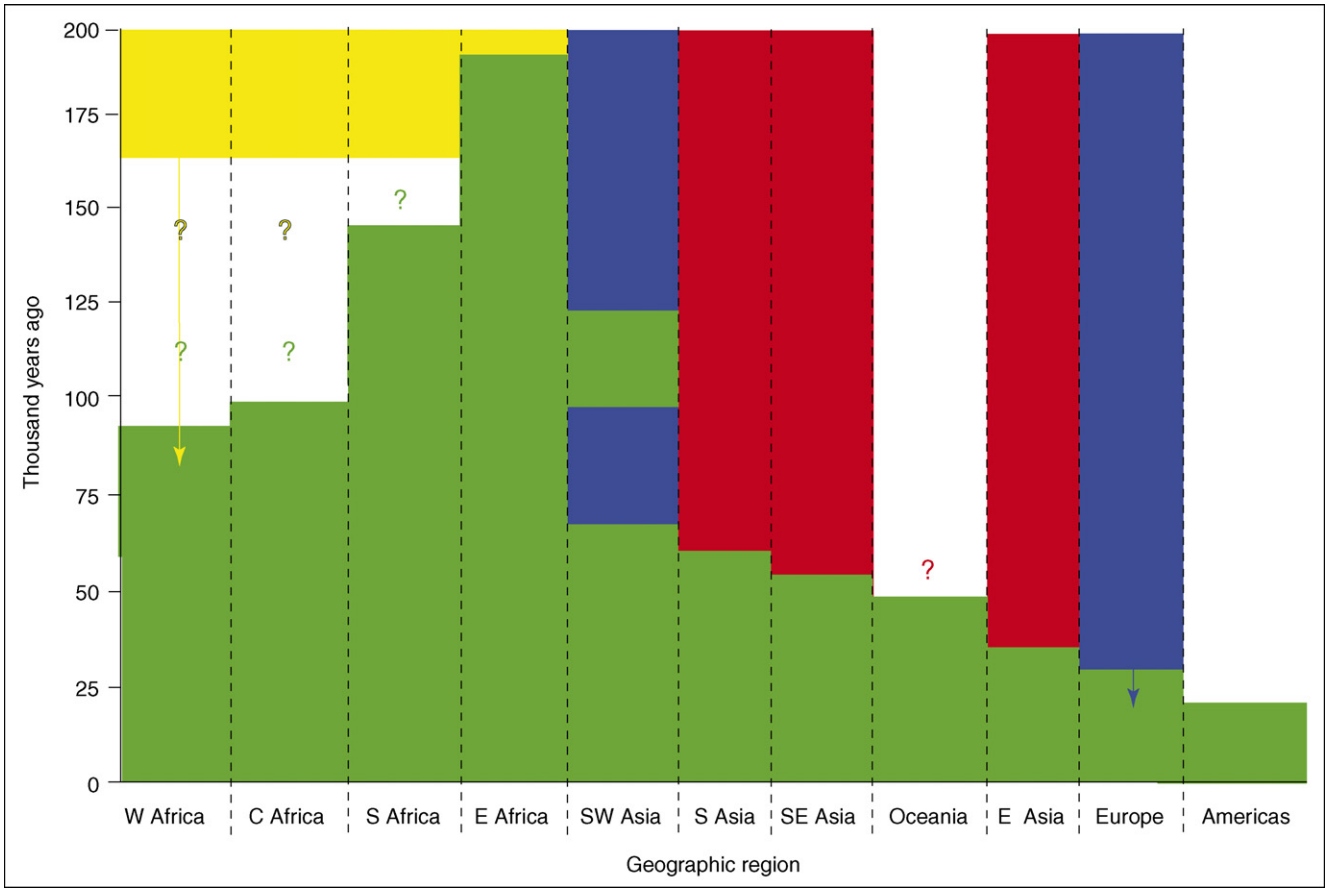
## Modern human origins in Africa

Human paleontology has established that humans have spread at least twice from Africa to Eurasia; early events involved archaic populations such as *Homo erectus* and *Homo heidelbergensis*, whereas a later event, occurring within the past 100 000 years, involved the migration of anatomically modern humans out of Africa and across the rest of the globe [5]. The transition to modern humans was unlikely to be sudden; rather, the paleobiological record indicates an irregular mosaic of modern, archaic and regional morphological and behavioral traits that occurred over a substantial period of time and across a broad geographic range within Africa [5,6]. The earliest known derived suite of morphological traits associated with modern humans appears in fossil remains from East Africa, dated to between 150 and 190 thousand years ago (kya) [7,8]. However, this does not rule out the existence of modern morphological traits in other regions of Africa before 100 kya, in regions where specimens might be less well preserved and/or where there have not been as extensive archaeological and paleobiological investigations. Indeed, a multiregional origin model for modern

humans within Africa is not as unlikely as it would be for global populations, considering the greater potential for migration and admixture within a single continental region. A more fully modern suite of traits appears in East Africa and Southwest Asia around 90 kya [9], followed by a rapid spread of modern humans throughout the rest of Africa and Eurasia in the past 40–80 thousand years (Figure 1) [10•].

Several recent genetic studies have used geographic information to determine the region of origin of modern humans within Africa. These studies have made use of the growing amount of microsatellite genotyping data available from the Centre d'Etude du Polymorphisme Humain (CEPH) human genome diversity panel (HGDP) [11]. Ray *et al.* [12•] explicitly modeled geographic distances, carrying capacities and migration rates across the Old World to test the ability to discriminate between single origin and multiple origin with migration models of human evolution and to infer the region of origin of modern humans. Ramachandran *et al.* [13•] took a simpler approach: assuming a serial founder effect as humans migrated away from a central point (see also [14,15]), they searched for the best-fitting point of origin given current levels of genetic variation and geographic distances of sampled populations. Although both of these studies solidly support Africa as the region of origin of modern humans, interestingly, they point to Northwest Africa [12•] and western to central Africa [13•], respectively, as the likely origin of modern humans before migration across the globe. It is intriguing to speculate that modern humans originated at a point outside of eastern or southern Africa, where the relatively rich fossil record indicates the first transition to modern humans took place.

**Figure 1**

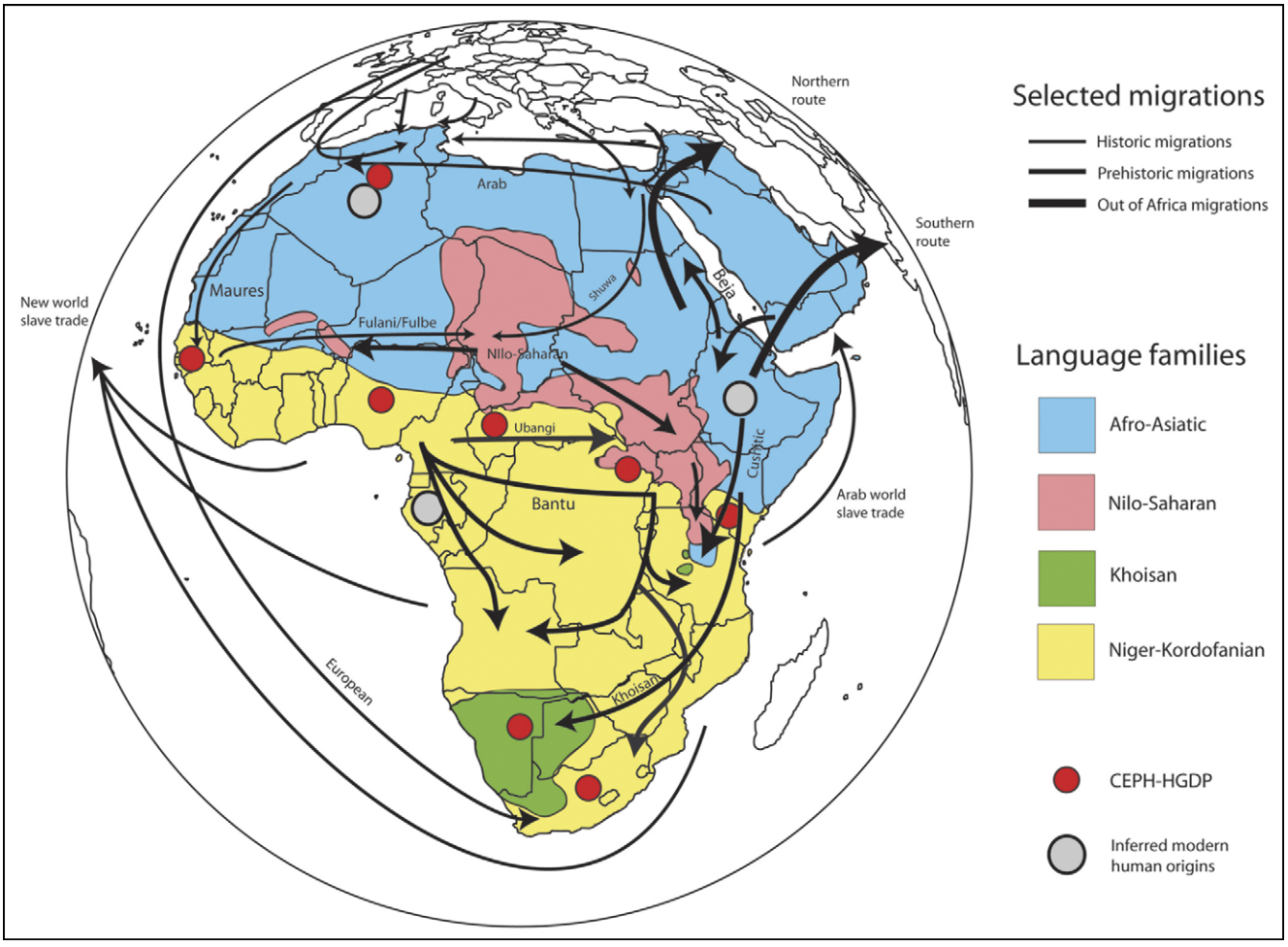



The emerging pattern of modern human expansion and admixture based on paleobiological, archeological and genetic data. The numbers on the left indicate thousands of years ago. Modern humans are indicated in green, Neanderthals in blue, Asian *Homo erectus* in red and archaic humans in Africa in yellow. After a transitional origin primarily in East Africa — but possibly including other regions — before 90–125 kya, and a brief expansion into Southwest Asia ~120 kya, modern humans quickly expanded into the rest of Africa, southern Asia and Oceania 50–70 kya, largely replacing archaic humans, and later spread further north in Asia, to Europe and the Americas from 30–40 kya. This representation does not include the persistence of isolated archaic humans in some regions such as Southeast Asia. Arrows indicate possible admixture events between modern and archaic humans.

There are two potential problems associated with the data used to make this inference: the first is ascertainment bias caused by selection of variable markers in a subset of populations (addressed by Ray *et al.* [12•]), and the second is the relative paucity of population samples within Africa (discussed by Ramachandran *et al.* [13•]). Some have argued that highly variable microsatellite markers are not influenced by ascertainment bias to the same extent as single nucleotide polymorphisms (SNPs) are [15,16]. However, assuming that these markers were selected because of their high heterozygosity in European populations, Ray *et al.* [12•] incorporated ascertainment bias into their analysis by selecting only simulated outcomes that have high heterozygosities in European populations. Upon re-analysis, they found more support for an east African origin, although support for a North African origin still remains high.

However, more information about how these markers were ascertained is needed to properly control for ascertainment bias. In fact, 60% of the markers (the GATA repeats) used in the Ray *et al.* [12•] study were ascertained in Europeans, but the remaining markers were ascertained in a worldwide panel (S Dobrin, personal communication), making control for ascertainment bias more complicated. The second potential problem with these studies is the sampling coverage of populations within Africa. Only eight population samples from Africa exist in the CEPH–HGDP collection after all the southern Bantu groups are pooled because of their small sample size (Figure 2) [11]. Only one of these is from East Africa, and it consists of a Kenyan Bantu-speaking population, which is likely to have a significant portion of ancestry originating from West Africa in the past few thousand years. Clearly, more population samples from all regions

**Figure 2**




A map of selected migrations and language family distributions in Africa. Languages change very rapidly over time, and a shared language family indicates some degree of recent shared cultural history. Hypothetical ancient migrations out of Africa are represented by the thickest arrows; more recent migrations in historical times are represented by thin arrows; inferred prehistoric migrations are represented by medium arrows; inferred regions of origin of modern humans are indicated by gray circles. Red circles indicate the geographic origin of cell lines in the CEPH–HGDP collection.

of Africa will increase the power to infer the most likely geographic origin of modern humans from genetic data.

## Evidence for admixture of archaic and modern *Homo* populations?

Overall, the weight of evidence from both genetic and paleobiological studies supports a recent common origin of all modern humans from a population originating from the continent of Africa — probably from East Africa — within the past 100 kya (summarized in [4]). Although analyses of ancient mtDNA obtained from 24 Neanderthal and 40 early modern human remains do not support high levels of admixture between archaic and modern humans [17], the possibility of limited gene flow is difficult to rule out [17–19]. Several recent studies of nucleotide sequence diversity at multiple autosomal [20••] and X chromosome [21•] loci have identified lineages with extensive linkage disequilibrium (LD) and ancient coalescence times, indicative of possible ancient population structure (throughout this review, we use the term population structure to refer to genetic heterogeneity resulting from non-random mating) followed by recent admixture (see the review by JD Wall and MF Hammer, this issue). Analyses of three 2.5-kb segments from the Xp21.1 region of the X chromosome found evidence consistent with ancient population structure in Africa extending over one million years into the past [21•]. A more recent study of 135 autosomal loci found evidence of a 5% level of archaic contributions to modern humans in both West Africa and Europe [20••]. These results raise the possibility of a small, but not insignificant, level of Neanderthal ancestry in modern Europeans, as well as possible admixture of archaic populations with modern humans in Africa [20••].

Evidence consistent with multiple archaic admixture events in the ancestors of modern humans is very intriguing. However, there is a possibility that unaccounted for factors such as selection and inversion polymorphisms might be contributing to a false 'archaic admixture' pattern seen in these gene regions. Inversion polymorphisms deserve a special note because they have the potential to create a very similar pattern of congruent SNPs and regions of high LD. Inversions of both short and long nucleotide sequences are a common feature of recent human evolution, and many inversions are polymorphic within modern humans [22,23•]. Inversions are known to suppress recombination [24,25•] and, therefore, the degree to which inversions might contribute to the inference of archaic admixture should be investigated. In addition, natural selection might be common in the genome and can influence inferred effective population sizes along the chromosomes, increasing the variance in expected coalescence times and creating a subset of regions with atypically ancient lineages [26•]. Furthermore, inversions have long been suspected to be directly affected by positive selection in other species [27,28], and examples of inversions under selection are beginning to be revealed in humans [25•]. Thus, both selection and inversion polymorphisms could be influencing patterns of LD, coalescence times, and inferences of ancient admixture events.

## A single African origin for non-African populations?

Estimates vary for the time of the first migration of modern humans from Africa to Eurasia. Paleontological data show modern humans in the Levant 90–130 kya, but it is not clear that this was a continuous occupation to the present. In general, age ranges inferred from mitochondrial DNA (mtDNA) suggest migrations out of Africa ~45–75 kya [10•,29], broadly consistent with dates inferred from paleontological [5], X chromosome [30], Y chromosome [31] and autosomal [32] data. However, inferences based on multiple independent markers, which will include more evolutionary information, will probably refine these estimates in the near future [14].

There have been two proposed migration routes of modern humans out of Africa. The early presence of modern humans in southern Asia and Oceania, predating their presence in Europe, has suggested a 'southern' coastal route around the Indian Ocean, in which modern humans first left Africa by crossing the Bab-el-Mandeb strait at the mouth of the Red Sea and then rapidly migrated to Southeast Asia. This migration model is supported by the presence of very old mtDNA haplotypes in South Asia and their absence in the Levant [10•,33,34]. A rapid coastal expansion of modern humans into Eurasia is feasible for several reasons. Coastal environments typically have more stable climates, and the exploitation of rich marine resources might have provided a more stable subsistence pattern around the Indian Ocean, enabling rapid migration. Indeed, as Macaulay *et al.* [10•] point out, humans were already exploiting marine resources on the coast of the Red Sea more than 100 kya [35]. There is also the suggestion, made on the basis of allele frequency gradients, that coastal habitats continued to be important centers of human expansion [36]. Others have traditionally favored a second (or single) 'northern' route via the Sinai Peninsula into the Levant. Regardless of the route of migration of modern humans out of Africa, the low level of mtDNA diversity — and also autosomal haplotype diversity at loci such as CD4 [32] — outside of Africa, and the high level of diversity amongst African populations, argues against a second 'sampling' of African diversity from multiple source populations, suggesting either a single major migration event out of Africa or multiple migrations from a single genetically homogeneous source population in Africa [4]. Analyses of more independent loci and a larger number of African populations, particularly from East Africa, will be necessary to better refine the number and source of migration events out of Africa.

How many modern humans were in that first wave of migration out of Africa? Modeling based on observed levels of mtDNA variability yields an estimate of only ~600 founding females [10•,37]. Thus, assuming an equal sex ratio, this implies that only ~1200 modern humans first left Africa to populate Eurasia. If this estimate is accurate, these early Eurasians must have rapidly expanded to a larger size to account for estimates of a long-term effective population size ($N_e$) of 10 000 individuals, especially given that $N_e$ is predicted to be the harmonic mean of sizes over time and is, thus, more influenced by small population sizes. Again, however, data from multiple independent loci should help to refine this picture in the near future; for example, a rapid expansion into newly colonized areas is supported by a recent analysis of 783 autosomal microsatellites genotyped in the CEPH-HGDP collection [14].

## Genetic adaptations

There have been some conflicting results regarding the relative amounts of recent positive selection in African versus non-African populations. It is easy to imagine an increase in positive selection as a species migrates into and adapts to new environments. Indeed, in addition to founder effects, novel selective demands have been suggested as a contributor to reductions of human genetic diversity outside of Africa [38]. Several studies in the past few years have reported more evidence for positive selection in populations outside of Africa relative to those in Africa [39•,40•,41–43]. However, this inference can be confounded by unknown demographic effects, and there are reasons to expect just as much or more selection within African populations. There have been dramatic changes in climate and subsistence patterns within Africa in the past 10 000 years, which have probably created similar demands for adaptation [2,44]. Furthermore, selection is predicted to act more efficiently and more frequently in African populations, owing to a larger effective population size and a greater amount of genetic diversity for selection to act upon [45,46]. Also, the rate of infectious disease in tropical Africa is very high and is a strong selective force that has resulted in clear patterns of selection at many loci associated with resistance to infectious disease (e.g. [47–50]). Indeed, a recent report that used a modified extended haplotype homozygosity (EHH) approach — sensitive to recent selective sweeps [48] — to scan the genome for regions under positive selection found evidence that more selection has occurred in the recent past within an African population compared with European and Asian populations [51••]. However, the robustness of the EHH tests to demographic scenarios (e.g. rapid population expansion after a bottleneck, particularly in the presence of population structure, which could cause a subset of haplotypes to rapidly drift to high frequency in a heterogeneous manner) needs to be established. Additionally, the role of inversion polymorphisms should again be considered. Inversions might suppress recombination over an extended region and, coupled with these types of complex demographic processes, might contribute to patterns of EHH similar to that observed under a model of positive selection.

## The African diaspora

In the United States alone, more than 36 million African Americans have recent origins in Africa (http://www.census.gov/population/www/socdemo/race/ppl-186.html), the majority of their ancestors having been forcibly brought to the Americas as slaves. Exact estimates vary, but according to analyses of historical records, the majority of the people brought to the Americas from Africa, approximately eight million, originated in western Africa, with a lesser amount, approximately four million, from central Africa; there was also a significant number, approximately one million, from Southeast Africa and the island of Madagascar [52]. Results of mtDNA genetic studies are broadly consistent with these historical origins [53]. Many African Americans, just like many European Americans, are interested in recovering part of their history by genetic analyses [54]. However, the informativeness of many commercial genetic genealogy test kits is limited and is often misunderstood by, or misrepresented to, the public. Studies based on mitochondrial or Y-chromosome variation only sample a single matrilineal or patrilineal ancestor out of the 1024 ancestors possible for a single individual just 10 generations ago (i.e. a sample of less then a thousandth of one's recent ancestry). Furthermore, even if a perfect match of mitochondrial sequence is found between an African American and an African individual, this does not conclusively establish descent from, or a unique connection to, a particular modern-day African ethnic group. For example, consider an analysis of nucleotide variation for 350 bp of the mitochondrial hypervariable region, where the effective per generation per bp mutation rate is approximately $2.5 \times 10^{-6}$. What is the probability that no mutations will occur between two individuals that descend from a common matrilineal ancestor? As a rough calculation, assuming a Poisson distribution, $P(0) = e^{-2\,\mu g}$, where $\mu$ is the mutation rate for the entire region, $g$ is the number of generations, and $P(0)$ is the probability that no mutations occur, it can be shown that even after 10 000 years, assuming 25 years per generation, there is an equal chance ($P(0) = 0.5$) of having an exact match. On average, more than 14 000 years ($g/2\,\mu$) will pass between each new mutation (assuming an exponential distribution); doubling the length sequenced will only cut these numbers in half to 5000 and 7000 years, respectively. Of course, this example is simplistic and ignores rate variation among sites, but these ages easily predate the origins of modern-day ethno-linguistic populations [55]. Further confounding the attempt to establish African American ancestry is the extensive population movements that have occurred in Africa, in both ancient and historical times (Figure 2), resulting in a broad geographic distribution of

many mitochondrial haplotypes within Africa [53,56]. Furthermore, genetic sampling is currently too sparse within Africa (e.g. regions such as Angola are largely unrepresented in genetic studies) to establish a baseline for comparison.

Analyses of large numbers of independent loci, more comprehensive sampling in Africa, and new statistical approaches will begin to yield more information about African American ancestry. However, this might be a daunting task. The preliminary finding, based on analysis of 372 autosomal microsatellite markers [57], of a low level of population structure (i.e. genetic homogeneity) among several Niger-Kordofanian-speaking western African populations suggests that resolving the individual ancestral contribution to African Americans will prove difficult. However, this preliminary finding needs to be confirmed by analysis of additional geographically diverse West African populations. Additionally, African Americans have, on average, approximately 20% European ancestry [54]. We might reasonably predict that just as many European Americans are descendants of many different ethnic groups within Europe, that African Americans will prove to be descended from many different populations within Africa (and Europe), and that a single unique connection to any single modern-day ethnicity, as many are currently seeking and are being sold, is not a realistic expectation.

## Biomedical implications

The continent of Africa is in dire need of safe and effective medical interventions. Deaths due to infectious disease are disproportionately higher in Africa then in any other region of the world. In addition to the one million deaths per year from malaria (http://www.cdc.gov/malaria/index.htm), the poor state of medical care in Africa has contributed to high rates of HIV infection, which in turn are promoting the spread of other serious diseases such as tuberculosis [58]. Furthermore, very little is known about genetic variation at loci involved in infectious disease susceptibility or resistance, and the genetic basis of disease across Africa.

The high level of genetic diversity in Africa also means that there is great potential to find genetic polymorphism at disease susceptibility loci in African populations. Knowledge of the genetic basis for resistance or susceptibility to infectious disease can guide research and medical intervention, and these benefits are not limited to African populations. Also, the field of pharmacogenetics, genetically based variable drug response, will benefit from the study of genetic variation at genes involved in drug metabolism [59]. Genetic distances within Africa can be as large as distances between other continental populations [4,60], yet the geographic and demographic boundaries of population structure in Africa remain essentially unknown. Such knowledge will be crucial for designing more effective pharmaceutical treatments on a regional scale and for designing association studies for mapping complex disease in African populations [1,4,61,62•].

Furthermore, there is interest in using the elevated levels of LD in recently admixed populations to map the genetic basis of complex diseases [62•]. Much of this focus has been on African Americans, and there has been recent success using this approach [62•]. Although several West African populations appear to have little genetic population structure, which adds to the utility of using a single West African population as a 'parental' baseline population in admixture mapping studies [57], it remains to be established whether 'coastal' Niger-Kordofanian-speaking West Africans sufficiently represent the African ancestry of African Americans. Again, more extensive sampling of African populations, and genotyping at hundreds, if not thousands, of independent loci is required to adequately characterize the ancestry of African Americans.

## Prospects

More comprehensive population sampling, maximizing both ethnic and geographic diversity, is needed to fully appreciate and study the genetic diversity contained in Africa. Eventually, publicly available cell lines should be established, under the appropriate ethical protocols, so that these samples can become a broad resource for the scientific community to complement the CEPH–HGDP.

A shift toward multilocus datasets, away from single-locus studies, holds great potential to refine our understanding of human demographic history. Also, a better understanding of the frequency, distribution and role of inversion polymorphisms on haplotype-based tests of neutrality and inferences of ancient population structure will be informative.

The recent accumulation of large, publicly available datasets on human genetic diversity, and the continued development of statistical and computational methods for inferring demographic history [20••,63], holds great potential to distinguish different models of modern human origins. Also, approaches that incorporate detailed geographic information such as natural boundaries (i.e. mountain ranges, rivers and deserts etc) in the inference of human demographic history might be informative [12•].

Recent advances in sequencing technology with small amounts of short fragments of DNA [64] will make analysis of ancient DNA, when present, more feasible, enabling researchers to test hypotheses of archaic admixture. However, analysis of one individual alone might have limited informativeness and, unfortunately, there is little hope of ancient DNA preservation in important regions such as the Tropics [65].

The development of high-throughput SNP genotyping methodologies (e.g. the Affymatrix 500K SNP chip), which are rapidly getting less expensive, will facilitate the possibility of doing whole-genome association studies of large number of Africans. These studies might have important implications for identifying genes that play a role in several common traits (e.g. height, weight, taste perception, blood pressure etc), as well as for identifying genes that play a role in resistance to infectious diseases such as HIV, malaria and TB. However, the challenging issues of ascertainment bias in SNP selection for these genotyping arrays must be overcome.

## Acknowledgements

Supported by a National Science Foundation grant BSC0552486 and National Institutes of Health (NIH) grant R01GM076637 to SAT, and NIH grant F32HG003801 to FAR.

### References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

1. Tishkoff SA, Williams SM: **Genetic analysis of African populations: human evolution and complex disease**. *Nat Rev Genet* 2002, **3**:611-621.

2. Kuper R, Kropelin S: **Climate-controlled Holocene occupation in the Sahara: motor of Africa's evolution**. *Science* 2006, **313**:803-807.

3. Tishkoff SA, Verrelli BC: **Patterns of human genetic diversity: implications for human evolutionary history and disease**. *Annu Rev Genomics Hum Genet* 2003, **4**:293-340.

4. Centers for Disease Control and Prevention (CDC): **The Global HIV/AIDS pandemic, 2006**. *MMWR Morb Mortal Wkly Rep* 2006, **55**:841-844.

5. Trinkaus E: **Early modern humans**. *Annu Rev Anthropol* 2005, **34**:207-230.

6. McBrearty S, Brooks A: **The revolution that wasn't: a new interpretation of the origin of modern human behavior**. *J Hum Evol* 2000, **39**:453-563.

7. White TD, Asfaw B, DeGusta D, Gilbert H, Richards GD, Suwa G, Howell FC: **Pleistocene *Homo sapiens* from Middle Awash, Ethiopia**. *Nature* 2003, **423**:742-747.

8. McDougall I, Fleagle JG: **Stratigraphic placement and age of modern humans from Kibish, Ethiopia**. *Nature* 2005, **433**:733-736.

9. McDermott F, Grun R, Stringer CB, Hawkesworth CJ: **Mass-spectrometric U-series dates for Israeli Neanderthal/early modern hominid sites**. *Nature* 1993, **363**:252-255.

10. • Macaulay V, Hill C, Achilli A, Rengo C, Clarke D, Meehan W, Blackburn J, Semino O, Scozzari R, Cruciani F *et al.*: **Single, rapid coastal settlement of Asia revealed by analysis of complete mitochondrial genomes**. *Science* 2005, **308**:1034-1036.
The authors find evidence consistent with the ideas that the first modern humans to leave Africa rapidly migrated along a southern coastal route and that modern humans have resided in Southeast Asia for a very long period of time, approximately 50 thousand years. The authors also estimate the size of the population that first left Africa as consisting of only a few hundred females.

11. Rosenberg NA, Pritchard JK, Weber JL, Cann HM, Kidd KK, Zhivotovsky LA, Feldman MW: **Genetic structure of human populations**. *Science* 2002, **298**:2381-2385.

12. • Ray N, Currat M, Berthier P, Excoffier L: **Recovering the geographic origin of early modern humans by realistic and spatially explicit simulations**. *Genome Res* 2005, **15**:1161-1167.
By combining geographic positions and evolutionary models that incorporate carrying capacities and migration rates, this study models the geographic spread of modern humans. Explicit geographic modelling is a promising approach that might see more development and implementation in the near future. An origin in East Africa is inferred once they account for ascertainment bias in their analysis.

13. • Ramachandran S, Deshpande O, Roseman CC, Rosenberg NA, Feldman MW, Cavalli-Sforza LL: **Support from the relationship of genetic and geographic distance in human populations for a serial founder effect originating in Africa**. *Proc Natl Acad Sci USA* 2005, **102**:15942-15947.
The authors find that levels of genetic variation are highly correlated with geographic distances, consistent with a gradual loss of genetic variation as humans diffused away from a point of origin. They then use this geographic relationship to infer the point of origin of all modern humans, which curiously points to west to central Africa.

14. Liu H, Prugnolle F, Manica A, Balloux F: **A geographically explicit genetic model of worldwide human-settlement history**. *Am J Hum Genet* 2006, **79**:230-237.

15. Harpending H, Rogers A: **Genetic perspectives on human origins and differentiation**. *Annu Rev Genomics Hum Genet* 2000, **1**:361-385.

16. Rogers AR, Jorde LB: **Ascertainment bias in estimates of average heterozygosity**. *Am J Hum Genet* 1996, **58**:1033-1041.

17. Serre D, Langaney A, Chech M, Teschler-Nicola M, Paunovic M, Mennecier P, Hofreiter M, Possnert G, Paabo S: **No evidence of Neandertal mtDNA contribution to early modern humans**. *PLoS Biol* 2004, **2**:E57.

18. Nordborg M: **On the probability of Neanderthal ancestry**. *Am J Hum Genet* 1998, **63**:1237-1240.

19. Wall JD: **Detecting ancient admixture in humans using sequence polymorphism data**. *Genetics* 2000, **154**:1271-1279.

20. •• Plagnol V, Wall JD: **Possible ancestral structure in human populations**. *PLoS Genet* 2006, **2**:e105.
This is a detailed and pragmatic treatment of a model of admixture between modern and archaic human populations. Using 135 autosomal loci, the authors estimate that 5% of the ancestors of modern Europeans and West Africans originate from human populations that were distinct from early modern humans.

21. • Garrigan D, Mobasher Z, Kingan SB, Wilder JA, Hammer MF: **Deep haplotype divergence and long-range linkage disequilibrium at Xp21.1 provide evidence that humans descend from a structured ancestral population**. *Genetics* 2005, **170**:1849-1856.
In this report, using data from a region on the X chromosome, a single panmictic ancestral population model is rejected for modern humans. The results suggest that modern humans are the result of admixture between distinct ancestral populations that might have diverged more than one million years ago.

22. She X, Jiang Z, Clark RA, Liu G, Cheng Z, Tuzun E, Church DM, Sutton G, Halpern AL, Eichler EE: **Shotgun sequence assembly and recent segmental duplications within the human genome**. *Nature* 2004, **431**:927-930.

23. • Feuk L, MacDonald JR, Tang T, Carson AR, Li M, Rao G, Khaja R, Scherer SW: **Discovery of human inversion polymorphisms by comparative analysis of human and chimpanzee DNA sequence assemblies**. *PLoS Genet* 2005, **1**:e56.
This study uses available genome sequences to establish that inversions are a common feature in human evolution and that many inversions are polymorphic among modern humans.

24. Jaarola M, Martin RH, Ashley T: **Direct evidence for suppression of recombination within two pericentric inversions in humans: a new sperm-FISH technique**. *Am J Hum Genet* 1998, **63**:218-224.

25. • Stefansson H, Helgason A, Thorleifsson G, Steinthorsdottir V, Masson G, Barnard J, Baker A, Jonasdottir A, Ingason A,

Gudnadottir VG *et al.*: **A common inversion under selection in Europeans**. *Nat Genet* 2005, **37**:129-137.
The authors find birth-rate differences that are associated with an inversion polymorphism. They suggest higher recombination rates and associated protection against aneuploidy in older mothers as a possible target of selection. However, it is also interesting to note that expression levels of *CRHR1* (*Corticotropin-releasing hormone receptor 1*), one of the genes in 17q21.31, is associated with pregnancy complications. If the inversion alleles affect expression levels of *CRHR1*, then this might have a direct effect on the average number of offspring of inversion carriers versus non-carriers.

26. • Reed FA, Akey JM, Aquadro CF: **Fitting background-selection predictions to levels of nucleotide variation and divergence along the human autosomes**. *Genome Res* 2005, **15**:1211-1221.
This study reveals significant evidence consistent with a general genome-wide role of selection in shaping levels of human genetic variation. Also, effective population sizes and the expected coalescent time-depth of lineages can vary substantially along the chromosomes, and modern polymorphism in some neutral genetic regions might predate the origins of our genus *Homo*.

27. Anderson PR, Knibb WR, Oakeshott JG: **Observations on the extent and temporal stability of latitudinal clines for alcohol dehydrogenase allozymes and four chromosome inversions in *Drosophila melanogaster***. *Genetica* 1987, **75**:81-88.

28. De Jong G, Bochdanovits Z: **Latitudinal clines in *Drosophila melanogaster*: body size, allozyme frequencies, inversion frequencies, and the insulin-signalling pathway**. *J Genet* 2003, **82**:207-223.

29. Ingman M, Kaessmann H, Paabo S, Gyllensten U: **Mitochondrial genome variation and the origin of modern humans**. *Nature* 2000, **408**:708-713.

30. Kaessmann H, Wiebe V, Weiss G, Paabo S: **Great ape DNA sequences reveal a reduced diversity and an expansion in humans**. *Nat Genet* 2001, **27**:155-156.

31. Underhill PA, Shen P, Lin AA, Jin L, Passarino G, Yang WH, Kauffman E, Bonne-Tamir B, Bertranpetit J, Francalacci P *et al.*: **Y chromosome sequence variation and the history of human populations**. *Nat Genet* 2000, **26**:358-361.

32. Tishkoff SA, Dietzsch E, Speed W, Pakstis AJ, Kidd JR, Cheung K, Bonne-Tamir B, Santachiara-Benerecetti AS, Moral P, Krings M: **Global patterns of linkage disequilibrium at the CD4 locus and modern human origins**. *Science* 1996, **271**:1380-1387.

33. Quintana-Murci L, Semino O, Bandelt HJ, Passarino G, McElreavey K, Santachiara-Benerecetti AS: **Genetic evidence of an early exit of *Homo sapiens sapiens* from Africa through eastern Africa**. *Nat Genet* 1999, **23**:437-441.

34. Thangaraj K, Chaubey G, Kivisild T, Reddy AG, Singh VK, Rasalkar AA, Singh L: **Reconstructing the origin of Andaman Islanders**. *Science* 2005, **308**:996.

35. Walter RC, Buffler RT, Bruggemann JH, Guillaume MM, Berhe SM, Negassi B, Libsekal Y, Cheng H, Edwards RL, von Cosel R *et al.*: **Early human occupation of the Red Sea coast of Eritrea during the last interglacial**. *Nature* 2000, **405**:65-69.

36. Amos W, Manica A: **Global genetic positioning: evidence for early human population centers in coastal habitats**. *Proc Natl Acad Sci USA* 2006, **103**:820-824.

37. Forster P, Matsumura S: **Evolution. Did early humans go north or south?** *Science* 2005, **308**:965-966.

38. Aquadro CF, Bauer DuMont V, Reed FA: **Genome-wide variation in the human and fruitfly: a comparison**. *Curr Opin Genet Dev* 2001, **11**:627-634.

39. • Stajich JE, Hahn MW: **Disentangling the effects of demography and selection in human history**. *Mol Biol Evol* 2005, **22**:63-73.
Using data from 151 gene regions in African Americans and European Americans, the authors show that the majority of non-equilibrium patterns present in the data can be explained by simple demographic processes. However, the correlation, found in Europeans, between skews in the mutational frequency spectrum and rates of recombination can only be explained with a genome-wide role of selection.

40. • Akey JM, Eberle MA, Rieder MJ, Carlson CS, Shriver MD, Nickerson DA, Kruglyak L: **Population history and natural selection shape patterns of genetic variation in 132 genes**. *PLoS Biol* 2004, **2**:E286.
This is an earlier study using data from 132 gene regions in the same samples as those of Stajich and Hahn [39•]. Once demographic processes are taken into account, there are several genes in the European sample — but not in the African American sample — with strong signals of positive selection. This drives the authors' conclusion that a higher rate of adaptation occurred as humans migrated out of Africa into new environments.

41. Hammer MF, Garrigan D, Wood E, Wilder JA, Mobasher Z, Bigham A, Krenz JG, Nachman MW: **Heterogeneous patterns of variation among multiple human X-linked Loci: the possible role of diversity-reducing selection in non-Africans**. *Genetics* 2004, **167**:1841-1853.

42. Kayser M, Brauer S, Stoneking M: **A genome scan to detect candidate regions influenced by local natural selection in human populations**. *Mol Biol Evol* 2003, **20**:893-900.

43. Storz JF, Payseur BA, Nachman MW: **Genome scans of DNA variability in humans reveal evidence for selective sweeps outside of Africa**. *Mol Biol Evol* 2004, **21**:1800-1811.

44. Wooding S, Kim UK, Bamshad MJ, Larsen J, Jorde LB, Drayna D: **Natural selection and molecular evolution in PTC, a bitter-taste receptor gene**. *Am J Hum Genet* 2004, **74**:637-646.

45. Kimura M: **Stochastic processes and distribution of gene frequencies under natural selection**. *Cold Spring Harb Symp Quant Biol* 1955, **20**:33-53.

46. Fisher RA: *The Genetical Theory of Natural Selection*. Oxford: Clarendon; 1930.

47. Tishkoff SA, Varkonyi R, Cahinhinan N, Abbes S, Argyropoulos G, Destro-Bisol G, Drousiotou A, Dangerfield B, Lefranc G, Loiselet J *et al.*: **Haplotype diversity and linkage disequilibrium at human G6PD: recent origin of alleles that confer malarial resistance**. *Science* 2001, **293**:455-462.

48. Sabeti PC, Reich DE, Higgins JM, Levine HZ, Richter DJ, Schaffner SF, Gabriel SB, Platko JV, Patterson NJ, McDonald GJ *et al.*: **Detecting recent positive selection in the human genome from haplotype structure**. *Nature* 2002, **419**:832-837.

49. Hamblin MT, Thompson EE, Di Rienzo A: **Complex signatures of natural selection at the Duffy blood group locus**. *Am J Hum Genet* 2002, **70**:369-383.

50. Wood ET, Stover DA, Slatkin M, Nachman MW, Hammer MF: **The β-globin recombinational hotspot reduces the effects of strong selection around HbC, a recently arisen mutation providing resistance to malaria**. *Am J Hum Genet* 2005, **77**:637-642.

51. •• Voight BF, Kudaravalli S, Wen X, Pritchard JK: **A map of recent positive selection in the human genome**. *PLoS Biol* 2006, **4**:e72.
The authors created a generalized EHH approach for use with single SNPs and applied this as a genome scan for recent, incomplete selective sweeps in three human populations. They found extensive evidence of recent positive selection in all three human populations and intriguingly little overlap in the genetic positions of inferred positive selection. This suggests that positive selection is a frequent occurrence in recent human evolution and that different populations might commonly have positive selection acting on different mutations. They also found stronger and more evidence for recent positive selection in African relative to European and Asian populations.

52. Thomas H: *The Slave Trade — The History of the Atlantic Slave Trade: 1440–1840* London: Macmillan; 1998.

53. Salas A, Richards M, Lareu MV, Scozzari R, Coppa A, Torroni A, Macaulay V, Carracedo A: **The African diaspora: mitochondrial DNA and the Atlantic slave trade**. *Am J Hum Genet* 2004, **74**:454-465.

54. Shriver MD, Kittles RA: **Genetic ancestry and the search for personalized genetic histories**. *Nat Rev Genet* 2004, **5**:611-618.

55. Nichols J: *Linguistic Diversity in Space and Time*. Chicago: University of Chicago Press; 1992.

56. Salas A, Richards M, De la Fe T, Lareu MV, Sobrino B, Sanchez-Diz P, Macaulay V, Carracedo A: **The making of**

**the African mtDNA landscape**. *Am J Hum Genet* 2002, **71**:1082-1111.

57. Adeyemo AA, Chen G, Chen Y, Rotimi C: **Genetic structure in four West African population groups**. *BMC Genet* 2005, **6**:38.

58. Corbett EL, Steketee RW, ter Kuile FO, Latif AS, Kamali A, Hayes RJ: **HIV-1/AIDS and the control of other infectious diseases in Africa**. *Lancet* 2002, **359**:2177-2187.

59. Roses AD: **Pharmacogenetics**. *Hum Mol Genet* 2001, **10**:2261-2267.

60. Tishkoff SA, Kidd KK: **Implications of biogeography of human populations for 'race' and medicine**. *Nat Genet* 2004, **36**:S21-S27.

61. Tishkoff SA, Verrelli BC: **Role of evolutionary history on haplotype block structure in the human genome: implications for disease mapping**. *Curr Opin Genet Dev* 2003, **13**:569-575.

62. Zhu X, Luke A, Cooper R, Quertermous T, Hains C, Mosley T,
• Gu C, Tang H, Rao D, Risch N *et al.*: **Admixture mapping for hypertension loci with genome-scan markers**. *Nat Genet* 2005, **37**:177-181.

A successful application of admixture mapping in African Americans to identify candidate chromosomal regions influencing susceptibility to an important and complex disease, hypertension.

63. Hey J, Nielsen R: **Multilocus methods for estimating population sizes, migration rates and divergence time, with applications to the divergence of *Drosophila pseudoobscura* and *D. persimilis***. *Genetics* 2004, **167**:747-760.

64. Noonan J, Hofreiter M, Smith D, Priest J, Rohland N, Rabeder G, Krause J, Detter J, Paabo S, Rubin E: **Genomic sequencing of Pleistocene cave bears**. *Science* 2005, **309**:597-599.

65. Reed FA, Kontanis EJ, Kennedy KA, Aquadro CF: **Ancient DNA prospects from Sri Lankan highland dry caves support an emerging global pattern**. *Am J Phys Anthropol* 2003, **121**:112-116.