Title

The great human expansion

Journal

Resonance, 24(6)

ISSN

0971-8044

Authors

Henn, Brenna M
Cavalli-Sforza, LL
Feldman, Marcus W

Publication Date

2019-06-01

DOI

10.1007/s12045-019-0830-4

Peer reviewed

The great human expansion

Brenna M. Henn[a], L. L. Cavalli-Sforza[a,1], and Marcus W. Feldman[b,2]

[a]*Department of Genetics, Stanford University School of Medicine, Stanford, CA 94305; and* [b]*Department of Biology, Stanford University, Stanford, CA 94305-5020*

Edited by C. Owen Lovejoy, Kent State University, Kent, OH, and approved September 25, 2012 (received for review July 19, 2012)

Genetic and paleoanthropological evidence is in accord that today's human population is the result of a great demic (demographic and geographic) expansion that began approximately 45,000 to 60,000 y ago in Africa and rapidly resulted in human occupation of almost all of the Earth's habitable regions. Genomic data from contemporary humans suggest that this expansion was accompanied by a continuous loss of genetic diversity, a result of what is called the "serial founder effect." In addition to genomic data, the serial founder effect model is now supported by the genetics of human parasites, morphology, and linguistics. This particular population history gave rise to the two defining features of genetic variation in humans: genomes from the substructured populations of Africa retain an exceptional number of unique variants, and there is a dramatic reduction in genetic diversity within populations living outside of Africa. These two patterns are relevant for medical genetic studies mapping genotypes to phenotypes and for inferring the power of natural selection in human history. It should be appreciated that the initial expansion and subsequent serial founder effect were determined by demographic and sociocultural factors associated with hunter-gatherer populations. How do we reconcile this major demic expansion with the population stability that followed for thousands years until the inventions of agriculture? We review advances in understanding the genetic diversity within Africa and the great human expansion out of Africa and offer hypotheses that can help to establish a more synthetic view of modern human evolution.

human population growth | hunter-gatherer demography | molecular evolution

Genetic data indicate that, approximately 45 to 60 kya, a very rapid population expansion occurred outside of Africa, and spread in all directions across the Eurasian continents, eventually populating the entire world. We dub this event the Great Expansion (Fig. 1). The precise location of the exit from Africa, and the relative timing of the southern coastal migration vs. the expansion into northern Eurasia, are still under intense debate (1–3). However, as we discuss here, many parameters of the Great Expansion are now well understood, including the general timing of the exit, the magnitude of the associated bottleneck, and the mode of subsequent expansion. We review the history of the Out of Africa (OOA) expansion, with an emphasis on recent genomic data, and highlight future avenues of research.

It is important first to distinguish between the presence of early near-modern humans in the Near East and the very distinct OOA exit associated with the Great Expansion. It is clear that anatomically near-modern humans occupied the Levant (4) during a warm interglacial period 130 to 80 kya, when this region was ecologically similar to northeastern Africa (5). However, current evidence indicates that this near-modern population did not persist in the Near East and was subsequently replaced by Neanderthals during the following glacial period, with little evidence of temporal overlap (5, 6). It is not until at least 50,000 y ago that evidence of behaviorally modern humans occurs in the archaeological record in the Near East. Only after this point do anatomically and behaviorally modern human remains become widespread in Eurasia. It is unclear what precipitated the tremendous population growth associated with this second occupation of the Near East and subsequent dispersal (7); possibly, cultural advances accumulated to a "tipping point" that supported extreme demographic growth (8), or anatomical changes that are not reflected in the paleoanthropological record [e.g., neuroanatomy (9)] occurred in the ancestral population. The geographic range expansions of humans outside of Africa were almost certainly associated with climatic fluctuations (10); however, the Great Expansion was an unprecedented demic success that occurred when the climate remained substantially colder than the previous interglacial. As discussed later, we know that the ancestral population for this expansion was African, but the rate of growth and structure of the ancestral population remain poorly understood.

An enormous wealth of genetic information about many populations has been generated in the century since the discovery of blood groups (11). The defining genetic feature of populations historically residing outside of Africa is the tremendous reduction in genetic diversity compared with populations residing in sub-Saharan Africa. Recent studies of autosomal polymorphisms are remarkably consistent in demonstrating the loss of diversity in OOA populations and in estimates of the parameters of this bottleneck (12–17) [also demonstrated clearly in the phylogenetic patterns of mtDNA and Y-chromsomal variation (18)]. Resequencing studies have estimated the ancestral effective population size at 12,800 to 14,400, with a 5- to 10-fold bottleneck beginning approximately 65,000 to 50,000 y ago (although see ref. 15 for a bottleneck to only 450 individuals). It is generally assumed that the bottleneck occurred as a small group(s) with an effective population size of only approximately 1,000 to 2,500 individuals moved from the African continent into the Near East. It should be noted that effective population sizes will generally be less than census population sizes, especially under extinction and recolonization (19).

The loss of genetic variation during the Great Expansion is assumed to have resulted from the way the world was settled by hunter-gatherer groups that, after colonizing a new habitat and expanding there, shed small groups that founded new colonies nearby. This genetic sampling process led to the successive reduction of variation in the newly founded colonies, with the reduction being proportional to the number of founders. A set of 52 populations from all continents [the Human Genetic Diversity Panel (20) has been studied with two large sets of markers: 784 microsatellites (21, 22) and 650,000 SNPs (23)]. In a single reasonably homogeneous population, genetic diversity of biparentally transmitted DNA can be assessed efficiently by counting heterozygotes for all variants. The pattern of average heterozygosities of today's populations suggest that, during the Great

Author contributions: B.M.H., L.L.C.-S., and M.W.F. designed research, performed research, analyzed data, and wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

[1]Present address: Faculty of Philosophy, Universita Vita-Salute San Raffaele, 20132 Milano, Italy.

[2]To whom correspondence should be addressed. E-mail: mfeldman@stanford.edu.

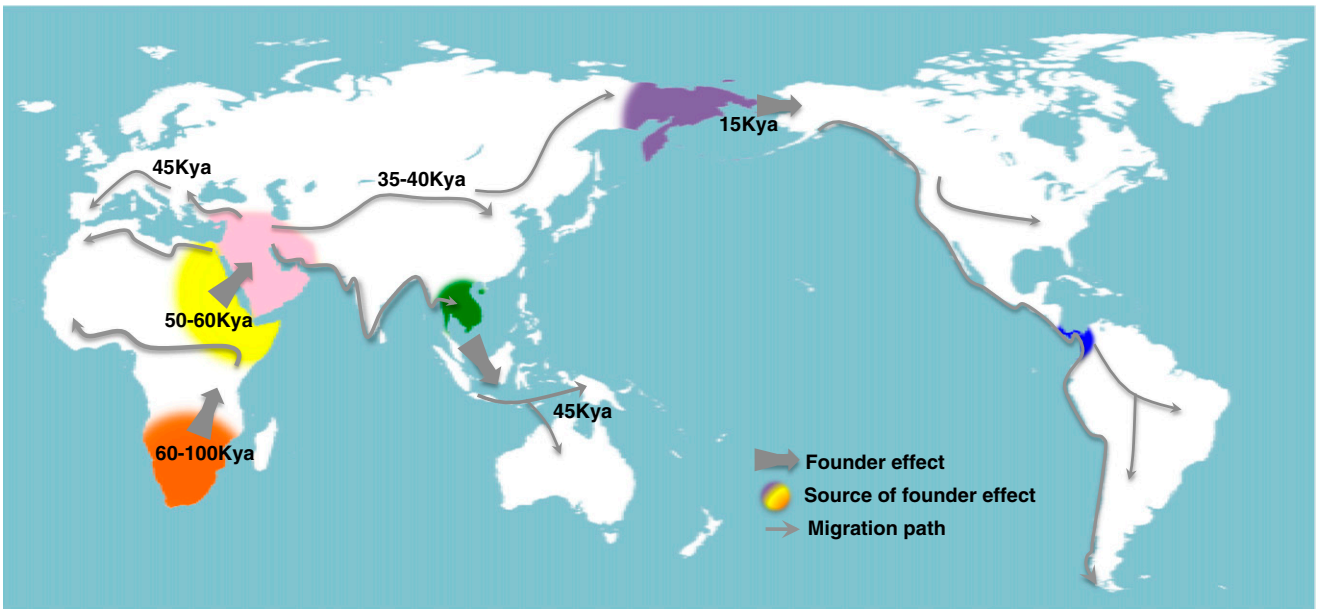

Fig. 1. Ancient dispersal patterns of modern humans during the past 100,000 y. This map highlights demic events that began with a source population in southern Africa 60 to 100 kya and conclude with the settlement of South America approximately 12 to 14 kya. Wide arrows indicate major founder events during the demographic expansion into different continental regions. Colored arcs indicate the putative source for each of these founder events. Thin arrows indicate potential migration paths. Many additional migrations occurred during the Holocene (11).

Expansion, there was a continuous decrease of genetic diversity with geographic distance from the place of origin in Africa (this takes account of the likely path of migration over land). The linear correlation between loss of genetic diversity and geographic distance from the origin of expansion in Africa is close to 90%.

The Great Expansion is thus consistent with serial colonization and concomitant loss of genetic heterozygosity, a process called a serial founder effect (Fig. 2) (21, 24, 25). A serial founder effect model involves three explicit assumptions. First, migration after the initial founder expansion was sufficiently limited that the populations in the series did not reach demographic equilibrium. This assumption appears warranted by the detectable substructure among continental and subcontinental populations throughout the globe (Fig. 1) (22, 23, 26–28). Second, the serial founder populations migrated into virgin territory or had no substantial admixture with other resident, and presumably divergent, populations. In the context of human evolution, admixture could potentially occur between humans and Neanderthals or other archaic species. Ancient DNA from Neanderthal and Denisova specimens remain subject to mixed interpretations. Ancient DNA sequences suggest that these hominin species were highly diverged from the ancestors of modern humans, more than 400 kya (29), and their unique haploid mtDNA and Y-chromosome signatures are not present among any modern humans (30, 31). On the contrary, analysis of several genomes indicated 1% to 7% differential archaic admixture among populations outside of Africa (32, 33). Importantly for the serial founder effect theory, a limited amount of archaic admixture does not destroy our power to detect a serial founder migration of the kind modeled for humans (24, 25). Archaic admixture of 10% or greater would produce a discontinuous relationship between heterozygosity and distance and inflate long-range linkage disequilibrium measures (24).

The third assumption is that there have been no dramatic postexpansion bottlenecks that differentially affected populations from which the serial migration began. If the source population for the expansion suffered a severe bottleneck that reduced its genetic diversity, we should see a poorer linear fit to the decline of heterozygosity with distance from Africa, or erroneously assign a population with higher genetic diversity as the source population. It is this third assumption we believe deserves additional consideration.

Human Origins in Africa

The African fossil record is consistent with a gradual accumulation of anatomically modern osteological features during 200 to 50 kya (34–37). By 195 to 160 kya, the Omo and Herto skulls from Ethiopia closely anticipate the form of contemporary humans, although they tend to be more robust overall. Multiple near-modern populations were present across the African continent at that time. This delay between the origin of the modern anatomical form and the successful expansion of humans ~100,000 y later has been the subject of intense paleoanthropological debate. Genetic data can directly address the time and rate of population growth in the African ancestral population; however, despite recent interest in this topic, current analyses are extremely limited and produce conflicting results.

Assuming a single step model of population growth and with full genome sequence data from one western African population (Yoruba), Gravel et al. (16) estimated a doubling in effective population size from approximately 7,000 to 14,000 that occurred 150 kya. Their model, however, did not separately account for more recent episodes of western African population growth that likely occur 30 to 40 kya and again at 5 kya (associated with the adoption of agriculture and subsequent expansion of Bantu-speaking agriculturalists) (38–41). Allowing for multiple episodes of population growth in the model would likely reduce the time of initial growth from 150 kya to a more recent estimate. In stark contrast, recent coalescent analysis of full genomic haplotypes within Yoruban individuals (17) estimates an effective population maximum occurring 50 to 150 kya, followed by bottleneck from which they begin to recover 40 kya. Two eastern African genomes from the Luhya and Maasai show an identical signal to the Yoruba, supporting a bottleneck model for all human populations between approximately 60 to 30 kya, whereby African populations experience a modest bottleneck and non-

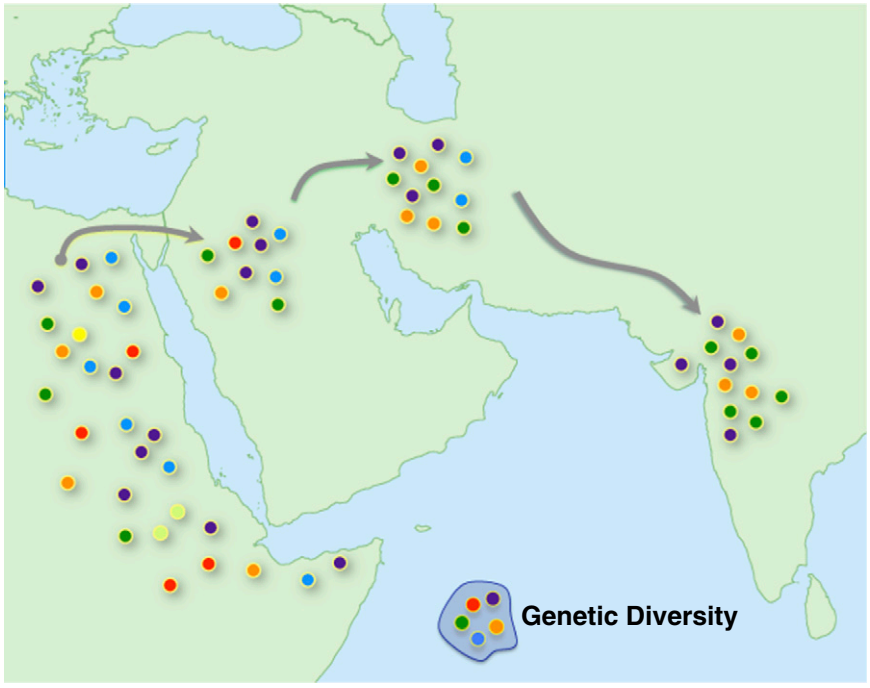

Fig. 2. Schematic of a serial found effect. We illustrate the effect of serial founder events on genetic diversity in the context of the OOA expansion. Colored dots indicate genetic diversity. Each new group outside of Africa represents a sampling of the genetic diversity present in its founder population. The ancestral population in Africa was sufficiently large to build up and retain substantial genetic diversity.

Africans a severe one (42). Coalescent analysis could be more sensitive to population structure than allele frequency-based estimates, which may help resolve the discrepancy between the two methods (see also ref. 43 for evidence of a 150-kya African bottleneck).

Unfortunately, genomic data from most populations in Africa remain limited. Whole mtDNA genomes suggest a low level of growth overall in Africa from 200 to 100 kya, but the timing of population growth estimated from mtDNA is sensitive to the geographic regions sampled. Southern Africa generally displays population stability while retaining a high estimated population size; western Africa shows multiple episodes of population growth, perhaps with the 30- to 50-kya period being the most relevant; and eastern Africa also displays marked population growth during this time period, potentially predating that in western Africa. A dramatic population growth signature is clearly evident only in L3 mitochondrial lineages likely originating in eastern Africa 60 to 85 kya (44, 45). Atkinson et al. (44) interpret this signature as evidence that population growth began in Africa, before the OOA expansion. It should be emphasized that these estimates have large error bounds and variation in parameter assumptions such as generation time and mutation rate are not fully incorporated. The mtDNA and (limited) autosomal data are not perfectly congruent regarding the timing of population growth and bottlenecks, in part because the same populations have not been surveyed for both mtDNA and autosomal loci. However, it is fair to say that estimates of divergence time among groups are generally more concordant.

For example, autosomal and X chromosome sequence data from five agricultural, four Western Pygmy, and three Eastern Pygmy populations produced an estimate of approximately 60 kya for the divergence of the farming and the hunter-gatherer groups and 20 kya for the separation of the two Pygmy populations (46). The estimated size of the population ancestral to all 12 sampled populations was approximately 7,000 to 15,000. This analysis also inferred population bottlenecks, with a decrease of 80% of the Western Pygmies between 2.5 and 25 kya, and a later 90% bottleneck of the Eastern Pygmies. [Cox et al. (47) obtained similar results with a smaller data set of autosomal sequences from fewer African populations.] Analysis of mtDNA variation in a different (but partially overlapping) set of Pygmy and farming populations produced similar divergence time estimates. However, estimates of the strength of population bottlenecks are greater with the autosomal and X chromosome data, and the timing of the bottlenecks in the Eastern Pygmies is estimated from mtDNA polymorphisms to have been earlier than that of the Western pygmies, reversing the order found with autosomal and X data (48). A third analysis (49) of microsatellite variation in Eastern Pygmies and farmers estimated a divergence time between these groups that was statistically similar to those found by using DNA sequence and mtDNA data.

In addition to the time of population growth, population substructure within Africa is important for fully understanding the OOA migration (50). Relative to populations outside of Africa, contemporary African populations retain an enormous amount of genetic variation. Furthermore, the genetic variation varies substantially from region to region as a result of the relatively deep substructure within Africa. Studies of patterns of autosomal DNA polymorphisms in present-day African hunter-gatherers show that they maintain exceptionally high genetic diversity, and several of these groups (e.g., KhoeSan, Hadza, Sandawe, Forest Pygmies) were the first to diverge from the ancestors that went on to become the larger agricultural groups in Africa and all populations outside Africa (27, 46, 51). In particular, the speakers of southern Khoisan or "click" languages (sometimes referred to as bushmen) show the greatest nucleotide diversity and the lowest association between pairs of nucleotides (i.e., linkage disequilibrium) along the same chromosome.

Henn et al. (51) showed a strong negative correlation within Africa of genetic diversity with distance from southwestern Africa, which is also consistent with a serial founder effect model for African populations. The initial divergence of African populations, inferred to be the separation between the ancestors of southern African KhoeSan and other Africans, was possibly twice as old as the time of the OOA migration (52). A recent study by Schlebusch et al. (53) analyzed genotype array data from additional samples of KhoeSan populations; they find linkage disequilibrium patterns to be more variable than reported by Henn et al. (51) and highlight the importance of recent demographic bottlenecks and agripastoralist migrations during the past 2,000 y. Gene flow between populations within Africa could have important effects on these estimates. However, coalescent analysis of their African dataset continue to support a model whereby the earliest population divergence is between KhoeSan and the rest of African populations approximately 100 kya. The time depth of substructure within Africa has been only minimally explored, and it will require more sophisticated methods to jointly estimate migration and divergence within a complex set of demes. That the southern African KhoeSan hunter-gatherers represent the most divergent group of Africans does not preclude an exit and subsequent expansion from northeastern Africa by

a group that eventually spread to all continents (54, 55) [although it is possible that North Africa may have been largely depopulated and resettled by OOA populations (56)]. Indeed, a serial founder model for Africa suggests a successive budding of populations as they moved into eastern, central, western, and eventually northern Africa (Fig. 1). Autosomal studies that estimate the time of divergence between African and OOA populations have almost exclusively used data from western Africans. However, a serial founder effect model predicts that different populations in Africa will produce different estimates of divergence between OOA populations.

An important assumption under the serial founder effect model, as mentioned earlier, is that subsequent population bottlenecks do not differentially affect populations near the origin of the expansion. It is possible that eastern African populations experienced a postexpansion bottleneck that decreased their diversity profile relative to other regions. The KhoeSan populations of southern Africa appear not to have contracted during the past 100,000 y or to have contracted minimally compared with other populations. (We note, however, that their present-day population numbers are dwindling.) Analysis of ancient DNA from eastern or northern African bones might establish that the genetic diversity was as great as that of present-day southern African KhoeSan populations. However, no ancient human DNA from Africa of great antiquity currently exists. From the currently available data, we conclude that the expansion of modern humans began within southern Africa and spread to other regions of Africa; then, a small group of humans exited northeastern Africa and continued this expansion throughout Eurasia, Oceania, and eventually the Americas.

Independent Evidence of Out of Africa Model

Human DNA variation is not the only evidence that supports a serial founder effect model OOA. Both *Plasmodium falciparum* (a malarial parasite) and *Helicobacter pylori* (a bacterium that occupies the human digestive tract) follow a strikingly similar pattern to the human DNA. The geographic pattern of *P. falciparum* genetic variation was found to be similar to that for humans, exhibiting a serial founder effect; forward simulations of the parasite's exit from Africa was estimated to be between 40 and 80 kya (depending on the assumed divergence rate from the chimpanzee parasite *Plasmodium reichenowi*) (57). *H. pylori* also shows a clear decline in genetic diversity with distance from eastern Africa, with an OOA estimate of 58 kya (58). [Interestingly, the most divergent and genetically diverse clade was from South Africa, although Linz et al. (58) eliminated this as an outlier in some analyses]. Even morphological variation of human crania supports a serial founder effect model OOA (59–61). In summary, multiple independent lines of genetic evidence thus support a serial founder effect mode of dispersal. Additionally, another large body of data may provide an independent test of the pattern of expansion and subsequent migrations around the globe: variation among languages.

Concordance Between Genes and Language. The evolution of languages is rapid—in a few hundred years, a language may change enough to destroy mutual understanding between neighboring populations, or even between ancestors and their descendants 1,000 y later. Families of languages that are similar enough that most linguists recognize them as such have a common origin in the range of 10,000 y ago. There is a remarkable similarity between the linguistic tree and the genetic tree, confirming Darwin's speculation that, if we knew the biological tree of humans, we could predict that of their languages (62). The first attempt to connect the two trees was made at a time when the linguistic tree was incomplete (63), but the similarity was clear and later shown to be statistically real (64). As might be expected, the geographical distribution of language families and that of genetic groupings of indigenous populations are also reasonably closely related.

Beyond congruence in phylogenetic topology, other aspects of genes and languages show correlations stemming from deep population processes. A recent analysis of phonemic diversity in 504 worldwide languages shows that this diversity exhibits the same serial founder effect discussed earlier for genetic variation, namely a loss of phonemic diversity proportional to distance from Africa (65). Moreover, within Africa, the greatest diversity is in the southern central region. Although the regression of phonemic diversity on distance from Africa is not as strong as seen with DNA polymorphisms, this finding nevertheless suggests that the genetic and linguistic expansion from Africa could have been part of the same process.

Ruhlen (66, 67) has extended greatly the linguistic tree that goes back to a single origin, and connects all 15 language families for which validity is fairly widely accepted. How do genetic data constrain a hypothesis of a single origin of modern language? Genetic evidence indicates that the vast majority of our ancestry is likely derived from a recent, common ancestral population that gave rise to modern humans (even estimates of archaic admixture remain very small). Even if African substructure dated back 100,000 y, most models indicate a single common ancestral population by 150,000 y (17). As all modern human populations maintain the ability to acquire and speak complex language, it is clear that, before the Great Expansion, language must have been fully developed in the ancestral population. Although it is unknown when language became fully developed, the necessary organs must have taken considerable time to reach the degree of complexity that is now common to the whole species. This includes the capacity to learn and use complicated syntax (perhaps completed even before 100,000 y ago and certainly before the origin of the Khoisan languages).

Demographic Models of OOA Expansion

Having established the basic pattern of the OOA expansion, we turn now to the local demographic processes that occurred during the expansion: how rapidly did population move across a geographic range, and what constraints on population growth seem likely from ethnographic studies? Deshpande et al. (25) simulated the serial founder effect process numerically, confirming that it is a good fit to worldwide autosomal microsatellite data. Archaeological information only approximates the precise route of the Great Expansion from its origin to its conclusion 25,000 km away, over a period of 50,000 y, so that the average rate of advance of 0.5 km/y or 15 km per generation on the most direct overland route is probably an underestimate. A minimum estimate of the number of colonization events that took place between these two extremes is then calculable from the average distance between two contiguous groups, which is approximately 140 km, or approximately 180 successive colonization events between the beginning and the end of the Great Expansion. With a rate of advance of 0.5 km/y, the time difference between successive colonization events is, on average, 280 y (approximately 10 generations). This gives an idea of the minimum time between one colonization and the next, and if we assume that, at the beginning of a new colony's life, the population doubles every generation, the rate of population increase must have decreased to zero when the new colony reached the stable size of 1,000 and produced a new colony. The simplest assumption for this process is logistic growth, beginning with doubling and a subsequently decreasing rate until the stable size is approached. However, there is considerable room for improvement of this type of simulation by incorporating more realistic migration, social structure, and even competition (68) among the simulated colonies.

The use of contemporary human genotypic variation to infer the time of onset and rate of expansion of the human population during the past 25,000 y has produced a wide range of estimates. Most studies that are based on sample sizes of less than 100 individuals place the onset of expansion of Europeans, for example, at 10 to 25 kya and subsequent growth at approximately 0.2% to 0.7% per generation (16, 38). These small sample sizes dictate that most of the variants detected must be at frequencies of 5% or higher. Recent analyses of next-generation sequence data in large samples of Europeans in the 2,000 to 10,000 range have detected many nucleotide variants that occur in only one or very few individuals (69–71). This distribution of rare alleles is compatible with explosive growth from the past 1,000 y at 9% per generation (69) or the past 5,000 y at 2% per generation (70). Ethnographic and archaeological evidence will be useful in providing known growth rates in historic populations. From genomic data, it appears safe to infer that the human population has recently expanded at a much faster exponential rate than was believed before the discovery of large numbers of rare variants.

However, genetic models tend to infer minimal population growth in most regions of the world between the OOA expansion and the last glacial period (approximately 21 kya). Additionally, most African populations appear to have remained relatively constant in size until the invention of agriculture in Africa and the associated growth and bottlenecks that occurred after 12 kya. How did human hunter-gatherer populations historically maintain stability? We consider two models, each of which could explain the apparent stability [see Read and LeBlanc (72) for additional hypotheses]. First, as a population enters a new, pristine environment, the birth rate rises as a result of the abundance of resources. Then, as growth occurs and the population increases in density, epidemiological risks also increase until there is a constant death rate over short or longer episodic time scales. Alternatively, the birth rate could be carefully regulated by cultural practices, and only allowed to exceed replacement when resources are abundant, for example, when a population moves into a new environment or when subsistence strategies improve.

Demography of Foragers

Why should population growth that occurred exponentially during the OOA expansion stop? The growth rate of a population is the difference between its birth rate and its death rate; the human birth rate is largely determined by the interaction between culturally transmitted customs (as detailed later) and resource limitations of the environment. When birth rates do not change, the change in growth after the population attains a stable size must be controlled by changes in the death rate. If the death rate is largely affected by disease, it is likely to be very low in a new environment, which is uncontaminated during the initial growth period and when the population density is low. We discuss the hypothesis that, as population density increases, the population increasingly contaminates its environment and has greater risk of communicable infectious disease and parasites.

Population Density. In a recent survey of 32 global hunter-gatherer populations, mean band size (i.e., the residential unit) averaged only 28 individuals (73). Bands are organized into larger interactive and reproductive units, sometimes referred to as tribes, among which dispersal occurs. Lee and DeVore (74) and Birdsell (75) proposed that surviving hunter-gatherer tribes have a fairly regular size of approximately 500. The dependence of population size on ecological conditions imposes limits on population density. Consider, for example, the tropical forest-dwelling central African Pygmies: population density estimated from ethnographic data on the Baka of Cameroon is 0.47 individuals per km^2 (or 35,000 individuals over 75,000 km^2) (76). The population density of western Pygmies in the Mbaiki area is even lower, 0.14 people per km^2. A hunter-gatherer family can travel approximately 50 km/d unloaded, and approximately 25 km/d loaded (estimated in a tropical forest environment). However, the effective dispersal distance between parents' place of birth and offsprings' place of birth among the Baka Pygmies is estimated to be only 12 to 64 km^2 (76). This is likely to be on the lower end of dispersal distances because it is derived from a population of forest-dwelling hunter-gatherers who today have extensive contact with farmers.

Although population density is often thought to be so low among hunter-gatherers that disease played little role in early human evolution, densities of the type observed among the central African Pygmies still affect spread of disease. The epidemiologists Pampiglione and Ricciardi (77) studied African Pygmies who live in camps in the forest when they hunt but spend part of the year in farmers' villages, during which they build their traditional huts in inconspicuous parts of the farmers' villages, behind the villagers' houses. Pygmies' huts are usually invisible from the main road, around which farmers' houses are built, often in one or a few rows on each side of the road. Even though farmers' wives frequently sweep to keep the soil in front of their houses clean, this soil is very highly contaminated with all sorts of potential pathogens. Most residents, and all Pygmies, walk with bare feet. In stool, urine, and other excrement of Pygmies and farmers, there is an extremely high load and great variety of parasites, with some difference between the two ethnic groups [mostly because of many parasites are acquired by Pygmies in the forest (77)]. Pygmy camps in the forest are sometimes built in fresh areas, but old camps are often reused. Such sanitary conditions are not limited to the denser population described in the forest environment. Among the Dobe !Kung in the Kalahari desert, Howell noted that individuals moved to a new camp site when their current site was considered contaminated by insects and excrement (78).

Many forms of infectious disease are also known to be density-dependent; as such, death rates from communicable infectious disease would also increase as populations established themselves in new environments. The frequency of infectious diseases among hunter-gatherers is difficult to estimate by using current ethnographies because the primary diseases often appear to be recently introduced. For example, although infectious and parasitic disease accounted for approximately 70% to 80% of deaths among the Dobe !Kung, tuberculosis, influenza, and sexually transmitted diseases are likely to only have been recently introduced (78). In the Hadza of Tanzania, approximately 45% of deaths from illness are ascribed to diseases that are likely recently introduced, such as tuberculosis and measles (79). When the Plains Native Americans' primary food source, bison, was eliminated, and they were moved to reservations where the population density increased, huge tuberculosis epidemics ensued (where the TB vector was originally transmitted from Europeans) (80, 81).

In summary, it seems reasonable to assume that, when a new colony is founded, its environment is reasonably clean and largely uncontaminated by human-specific diseases. Under these conditions, death rates are lowest and the population grows at a fairly high rate. However, as parasites brought in by the colonizers multiply and are spread through the camp or village environment, contamination grows and death rates increase. We note that the death rate need not be constant to produce apparently long-term population stability; episodic epidemiological catastrophes could also act to reduce population sizes.

Culturally Mediated Population Stability. Social customs can affect birth rate in the few hunter-gatherer groups that have been investigated, and these may have been inherited from the ancestral population. One such custom is that women may stop

having children 10 to 12 years before biological menopause. At least in central African Pygmies, women stop reproducing when their first daughter has a child (82). This custom tends to limit the number of children born per family to six or seven, and approximately two thirds of these die before reproduction, so only approximately two children per family survive to reproduce, and population size remains constant. Mace and Alvergne (83) show that a similar phenomenon occurs among Gambian agriculturalists; as reproductive spans overlap between mothers and daughters, mothers reduce their fertility when their daughters begin have their own children, even if the daughters are dispersed outside their natal home. This custom of premature menopause also has the property of being elastic and responding to changes in death rates of the young. More detailed research is needed to test whether this cultural menopause fluctuates with death rates in families. Another custom that limits birth rates derives from spacing births by extending lactation over a period of 3 or 4 y. This occurs in part because a child can only walk with parents during transitions from one territory to another after (s)he is approximately 4 y of age—otherwise (s)he has to be carried by one of the parents, who already have a heavy load of hunting and cooking tools. Finally, we note that delaying the age at first marriage is an important cultural custom, which tends to reduce overall fertility. We stress that fertility rates among hunter-gatherer populations are not uniform, total fertility rates vary from 4.7 to 8.2 depending on the population (79).

In summary, we have suggested that, during the Great Expansion, birth rate may have been more culturally regulated than the death rate, which is more constrained by biological phenomena. Additionally, these two rates may have opposite patterns of stability. As populations disperse into new, abundant environments, the birth rate may increase initially and then eventually stabilize if resources are limited by density. The death rate, however, will remain low after the founding of a new colony, and, although it is smaller than the birth rate at the beginning of growth, it will then increase as a result of epidemiological stresses, which can result from a contaminated environment and/or increased population density. Therefore, after several generations, a new colony can reach and maintain a constant population size. There may be other cultural customs and biological constraints than those mentioned earlier that may help to stabilize the size of a hunter-gatherer group at its apparent optimum value. The genetic studies referred to here suggest that modern human populations experienced long-term population stability for thousands of years (between 45,000 ya and 15,000 ya) with changes in growth rate primarily linked to the adoption of agropastoralism during the Holocene (38).

Conclusions

Human genetic, linguistic, and phenotypic data strongly support a serial founder effect model for the Great Expansion OOA approximately 45 to 60 kya. Significant gaps in our knowledge of human population history still exist. Additional sampling and sequencing of African populations remains a priority to address the number of African exits, the depth of substructure among African populations and differential geographic pattern of population bottlenecks (with implications for the location of origin within Africa). In addition, refined measures of environmental variability and its temporal/spatial changes across Africa would help clarify when human dispersals were likely. Computational models incorporating multiple episodes of growth and capable of inferring migration/divergence among more than three demes will need to be developed for this next wave of genomic data. We stress, however, that a synthesis among genetic, demographic, and anthropological models is important for a full understanding of many parameters of human prehistory, as illustrated here with population stability. For example, studies of natural selection could pair selection statistics with current phenotypic data, and model the time of selective pressure based on archeological information. Many genetic projects still ignore the rich background of archaeological and ethnographic data when testing genetic models, or tend to highlight only those findings that are consistent with the genetic conclusions. Information from all of the sources mentioned here will be necessary to constrain the complex hypotheses surrounding modern human origins.

ACKNOWLEDGMENTS. The authors thank Christopher Gignoux for assistance in creating the map (Fig. 1). This research was supported in part by National Institutes of Health Grants GM28016, HG003329, and 3R01HG003229.

1. Oppenheimer S (2012) A single southern exit of modern humans from Africa: Before or after Toba? *Quat Int* 258: 88–99.
2. Rasmussen M, et al. (2011) An Aboriginal Australian genome reveals separate human dispersals into Asia. *Science* 334(6052):94–98.
3. Macaulay V, et al. (2005) Single, rapid coastal settlement of Asia revealed by analysis of complete mitochondrial genomes. *Science* 308(5724):1034–1036.
4. Bar-Yosef O (2000) The Middle and early Upper Paleolithic in Southwest Asia and neighboring regions. *The Geography of Neandertals and Modern Humans in Europe and the Greater Mediterranean*, eds Bar-Yosef O, Pilbeam D (Peabody Museum Press, Cambridge, MA), pp 107–156.
5. Klein R (2009) *The Human Career: Human Biological and Cultural Origins* (Univ Chicago Press, Chicago).
6. Hodgson JA, Bergey CM, Disotell TR (2010) Neandertal genome: The ins and outs of African genetic diversity. *Curr Biol* 20(12):R517–R519.
7. Mellars P (2006) Why did modern human populations disperse from Africa ca. 60,000 years ago? A new model. *Proc Natl Acad Sci USA* 103(25):9381–9386.
8. Mcbrearty S, Brooks AS (2000) The revolution that wasn't: A new interpretation of the origin of modern human behavior. *J Hum Evol* 39(5):453–563.
9. Klein RG (2003) Paleoanthropology. Whither the Neanderthals? *Science* 299(5612):1525–1527.
10. Stewart JR, Stringer CB (2012) Human evolution out of Africa: The role of refugia and climate change. *Science* 335(6074):1317–1321.
11. Cavalli-Sforza LL, Menozzi P, Piazza A (1994) *The History and Geography of Human Genes* (Princeton Univ Press, Princeton).
12. McEvoy BP, Powell JE, Goddard ME, Visscher PM (2011) Human population dispersal "Out of Africa" estimated from linkage disequilibrium and allele frequencies of SNPs. *Genome Res* 21(6):821–829.
13. Amos W, Hoffman JI (2010) Evidence that two main bottleneck events shaped modern human genetic diversity. *Proc Biol Sci* 277(1678):131–137.
14. Laval G, Patin E, Barreiro LB, Quintana-Murci L (2010) Formulating a historical and demographic model of recent human evolution based on resequencing data from noncoding regions. *PLoS ONE* 5(4):e10284.
15. Fagundes NJR, et al. (2007) Statistical evaluation of alternative models of human evolution. *Proc Natl Acad Sci USA* 104(45):17614–17619.
16. Gravel S, et al; 1000 Genomes Project (2011) Demographic history and rare allele sharing among human populations. *Proc Natl Acad Sci USA* 108(29):11983–11988.
17. Li H, Durbin R (2011) Inference of human population history from individual whole-genome sequences. *Nature* 475(7357):493–496.
18. Underhill PA, Kivisild T (2007) Use of y chromosome and mitochondrial DNA population structure in tracing human migrations. *Annu Rev Genet* 41:539–564.
19. Eller E, Hawks J, Relethford JH (2004) Local extinction and recolonization, species effective population size, and modern human origins. *Hum Biol* 76:789–809.
20. Cann HM, et al. (2002) A human genome diversity cell line panel. *Science* 296(5566):261–262.
21. Ramachandran S, et al. (2005) 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* 102(44):15942–15947.
22. Rosenberg NA, et al. (2002) Genetic structure of human populations. *Science* 298(5602):2381–2385.
23. Li JZ, et al. (2008) Worldwide human relationships inferred from genome-wide patterns of variation. *Science* 319(5866):1100–1104.
24. DeGiorgio M, Jakobsson M, Rosenberg NA (2009) Out of Africa: Modern human origins special feature: explaining worldwide patterns of human genetic variation using a coalescent-based serial founder model of migration outward from Africa. *Proc Natl Acad Sci USA* 106(38):16057–16062.
25. Deshpande O, Batzoglou S, Feldman MW, Cavalli-Sforza LL (2009) A serial founder effect model for human settlement out of Africa. *Proc Biol Sci* 276 (1655):291–300.
26. Henn BM, Gravel S, Moreno-Estrada A, Acevedo-Acevedo S, Bustamante CD (2010) Fine-scale population structure and the era of next-generation sequencing. *Hum Mol Genet* 19(R2):R221–R226.
27. Tishkoff SA, et al. (2009) The genetic structure and history of Africans and African Americans. *Science* 324(5930):1035–1044.
28. Vigilant L, Stoneking M, Harpending H, Hawkes K, Wilson AC (1991) African populations and the evolution of human mitochondrial DNA. *Science* 253(5027): 1503–1507.

29. Endicott P, Ho SYW, Stringer C (2010) Using genetic evidence to evaluate four palaeoanthropological hypotheses for the timing of Neanderthal and modern human origins. *J Hum Evol* 59(1):87–95.
30. Ghirotto S, Tassi F, Benazzo A, Barbujani G (2011) No evidence of Neandertal admixture in the mitochondrial genomes of early European modern humans and contemporary Europeans. *Am J Phys Anthropol* 146(2): 242–252.
31. Krause J, et al. (2010) The complete mitochondrial DNA genome of an unknown hominin from southern Siberia. *Nature* 464(7290):894–897.
32. Green RE, et al. (2010) A draft sequence of the Neandertal genome. *Science* 328(5979):710–722.
33. Reich D, et al. (2010) Genetic history of an archaic hominin group from Denisova Cave in Siberia. *Nature* 468(7327):1053–1060.
34. Bräuer G (2008) The origin of modern anatomy: by speciation or intraspecific evolution? *Evol Anthropol* 17:22–37.
35. Pearson OM (2008) Statistical and biological definitions of "anatomically modern" humans: Suggestions for a unified approach to modern morphology. *Evol Anthropol* 17:38–48.
36. Weaver TD (2012) Did a discrete event 200,000-100,000 years ago produce modern humans? *J Hum Evol* 63(1): 121–126.
37. McDougall I, Brown FH, Fleagle JG (2005) Stratigraphic placement and age of modern humans from Kibish, Ethiopia. *Nature* 433(7027):733–736.
38. Gignoux CR, Henn BM, Mountain JL (2011) Rapid, global demographic expansions after the origins of agriculture. *Proc Natl Acad Sci USA* 108(15):6044–6049.
39. Marth GT, Czabarka E, Murvai J, Sherry ST (2004) The allele frequency spectrum in genome-wide human variation data reveals signals of differential demographic history in three large world populations. *Genetics* 166(1):351–372.
40. Voight BF, et al. (2005) Interrogating multiple aspects of variation in a full resequencing data set to infer human population size changes. *Proc Natl Acad Sci USA* 102(51):18508–18513.
41. Zhivotovsky LA, Rosenberg NA, Feldman MW (2003) Features of evolution and expansion of modern humans, inferred from genomewide microsatellite markers. *Am J Hum Genet* 72(5):1171–1186.
42. Kidd JM, et al. (2012) Population genetic inference from personal genome data: Impact of ancestry and admixture on human genomic variation. *Am J Hum Genet* 91:660–671.
43. Blum MGB, Jakobsson M (2011) Deep divergences of human gene trees and models of human origins. *Mol Biol Evol* 28(2):889–898.
44. Atkinson QD, Gray RD, Drummond AJ (2009) Bayesian coalescent inference of major human mitochondrial DNA haplogroup expansions in Africa. *Proc Biol Sci* 276(1655):367–373.
45. Soares P, et al. (2012) The Expansion of mtDNA Haplogroup L3 within and out of Africa. *Mol Biol Evol* 29 (3):915–927.
46. Patin E, et al. (2009) Inferring the demographic history of African farmers and pygmy hunter-gatherers using a multilocus resequencing data set. *PLoS Genet* 5(4): e1000448.
47. Cox MP, et al. (2009) Autosomal resequence data reveal Late Stone Age signals of population expansion in sub-Saharan African foraging and farming populations. *PLoS ONE* 4(7):e6366.
48. Batini C, et al. (2011) Insights into the demographic history of African Pygmies from complete mitochondrial genomes. *Mol Biol Evol* 28(2):1099–1110.
49. Verdu P, et al. (2009) Origins and genetic diversity of pygmy hunter-gatherers from Western Central Africa. *Curr Biol* 19(4):312–318.
50. Harding RM, McVean G (2004) A structured ancestral population for the evolution of modern humans. *Curr Opin Genet Dev* 14(6):667–674.
51. Henn BM, et al. (2011) Hunter-gatherer genomic diversity suggests a southern African origin for modern humans. *Proc Natl Acad Sci USA* 108(13):5154–5162.
52. Gronau I, Hubisz MJ, Gulko B, Danko CG, Siepel A (2011) Bayesian inference of ancient human demography from individual genome sequences. *Nat Genet* 43 (10):1031–1034.
53. Schlebusch CM, et al. (2012) Genomic variation in seven Khoe-San groups reveals adaptation and complex African history. *Science*, 10.1126/science.1227721.
54. Henn BM, Bustamante CD, Mountain JL, Feldman MW (2011) Reply to Hublin and Klein: Locating a geographic point of dispersion in Africa for contemporary humans. *Proc Natl Acad Sci USA* 108:E278.
55. Hublin JJ, Klein RG (2011) Northern Africa could also have housed the source population for living humans. *Proc Natl Acad Sci USA* 108(28):E277.
56. Henn BM, et al. (2012) Genomic ancestry of North Africans supports back-to-Africa migrations. *PLoS Genet* 8(1): e1002397.
57. Tanabe K, et al. (2010) Plasmodium falciparum accompanied the human expansion out of Africa. *Curr Biol* 20 (14):1283–1289.
58. Linz B, et al. (2007) An African origin for the intimate association between humans and Helicobacter pylori. *Nature* 445(7130):915–918.
59. Betti L, Balloux F, Amos W, Hanihara T, Manica A (2009) Distance from Africa, not climate, explains within-population phenotypic diversity in humans. *Proc Biol Sci* 276(1658):809–814.
60. Manica A, Amos W, Balloux F, Hanihara T (2007) The effect of ancient population bottlenecks on human phenotypic variation. *Nature* 448(7151):346–348.
61. von Cramon-Taubadel N, Lycett SJ (2008) Brief communication: Human cranial variation fits iterative founder effect model with African origin. *Am J Phys Anthropol* 136(1):108–113.
62. Darwin C (1860) *The Origin of Species* (John Murray, London), 2nd Ed, Chap 14, pp 392–393.
63. Cavalli-Sforza LL, Piazza A, Menozzi P, Mountain J (1988) Reconstruction of human evolution: Bringing together genetic, archaeological, and linguistic data. *Proc Natl Acad Sci USA* 85(16):6002–6006.
64. Cavalli-Sforza LL, Minch E, Mountain JL (1992) Coevolution of genes and languages revisited. *Proc Natl Acad Sci USA* 89(12):5620–5624.
65. Atkinson QD (2011) Phonemic diversity supports a serial founder effect model of language expansion from Africa. *Science* 332(6027):346–349.
66. Gell-Mann M, Ruhlen M (2011) The origin and evolution of word order. *Proc Natl Acad Sci USA* 108(42): 17290–17295.
67. Ruhlen M (1994) *The Origin of Language: Tracing the Evolution of the Mother Tongue* (Wiley, New York).
68. Hamilton MJ, et al. (2009) Population stability, cooperation, and the invasibility of the human species. *Proc Natl Acad Sci USA* 106(30):12255–12260.
69. Coventry A, et al. (2010) Deep resequencing reveals excess rare recent variants consistent with explosive population growth. *Nat Commun* 1:131.
70. Tennessen JA, et al; Broad GO; Seattle GO; NHLBI Exome Sequencing Project (2012) Evolution and functional impact of rare coding variation from deep sequencing of human exomes. *Science* 337(6090):64–69.
71. Keinan A, Clark AG (2012) Recent explosive human population growth has resulted in an excess of rare genetic variants. *Science* 336(6082):740–743.
72. Read DW, LeBlanc SA (2003) Population growth, carrying capacity, and conflict. *Curr Anthropol* 44:59–85.
73. Hill KR, et al. (2011) Co-residence patterns in hunter-gatherer societies show unique human social structure. *Science* 331(6022):1286–1289.
74. Lee RB, DeVore I, eds (1968) *Man the Hunter* (Aldine, Chicago).
75. Birdsell JB (1973) A basic demographic unit. *Curr Anthropol* 14:337–356.
76. Verdu P, et al. (2010) Limited dispersal in mobile hunter-gatherer Baka Pygmies. *Biol Lett* 6(6):858–861.
77. Pampiglione S, Ricciardi ML (1986) Parasitological surveys of Pygmy groups. *African Pygmies*, ed Cavalli-Sforza LL (Academic, New York), pp 153–165.
78. Howell N (1979) *Demography of the Dobe !Kung* (Academic, New York).
79. Blurton Jones NG, Hawkes K, O'Connell JF (2002) Antiquity of postreproductive life: Are there modern impacts on hunter-gatherer postreproductive life spans? *Am J Hum Biol* 14(2):184–205.
80. Ferguson R (1928) *Tuberculosis Among the Indians of the Great Canadian Plains* (Adlard, London).
81. Pepperell CS, et al. (2011) Dispersal of *Mycobacterium tuberculosis* via the Canadian fur trade. *Proc Natl Acad Sci USA* 108(16):6526–6531.
82. Hewlett BS, Hewlett BL (2010) Sex and searching for children among Aka foragers and Ngandu farmers of Central Africa. *Afr Study Monogr* 31:107–125.
83. Mace RH, Alvergne A (2012) Female reproductive competition within families in rural Gambia. *Proc R Soc B Biol Sci* 279(1736):2219–2227.