Sex-biased migration in humans: what should we expect from genetic data?

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Summary

Different patterns of mitochondrial and Y-chromosome diversity have been cited as evidence of long-term patrilocality in human populations. However, what patterns are expected depends on the nature of the sampling scheme. Samples from a local region reveal only the recent demographic history of that region, whereas sampling over larger geographic scales accesses older demographic processes. A historical change in migration becomes evident first at local geographic scales, and alters global patterns of genetic diversity only after sufficient time has passed. Analysis of forager populations in the ethnographic record suggests that patrilocality may not have predominated among pre-agricultural humans. The higher female migration rate inferred by some genetic studies may reflect a shift to patrilocality in association with the emergence of agriculture. A recent global survey does not show the expected effects of higher female migration, possibly because the sampling scheme used for this study is accessing pre-agricultural human migration patterns. In this paper, we show how the demographic shift associated with agriculture might affect genetic diversity over different spatial scales. We also consider the prospects for studying sex-biased migration using the X-linked and autosomal markers. These multi-locus comparisons have the potential of providing more robust estimates of sex differences than Y-linked and mitochondrial data, but only if a very large number of loci are included in the analysis. ***BioEssays*** **28:290–300, 2006. © 2006 Wiley Periodicals, Inc.**

Introduction

Sex-biased dispersal is found in many animals, including humans. Current patterns of dispersal can often be studied through direct observation—by tracking the movements of individual males and females. Studying dispersal patterns in the past, however, typically relies on indirect methods, such as analysis of archaeological or genetic data. In recent years, genetic methods have been employed in an effort to quantify the differences between the migration histories of human males and females. For the most part, these efforts have focused on two chromosomes: the mitochondria (mtDNA) and the non-recombining portion of the Y-chromosome (NRY), which both have special, uni-parental modes of inheritance. Because the mtDNA is always inherited from the mother, it reflects the demographic history of females, whereas the paternally inherited NRY reflects the demographic history of males.

In 1998, Seielstad and colleagues published the first global comparison of human mtDNA and NRY diversity.[1] Using a simple model of geographic structure—and a number of other simplifying assumptions—this analysis suggested that the female migration rate was approximately eight times greater than that for males. The difference was attributed to the predominance of patrilocality among human cultures: it is far more common for a wife to move in with her husband's family, or into his village, than the other way around. Under patrilocality, the typical distance between the birthplaces of a father and his sons is smaller than that between a mother and her daughters. Over the course of many generations, this produces systematic differences in the patterns of geographic diversity on the mtDNA and NRY, which we can observe today.

Since the publication of the original Seielstad study, a large number of studies comparing the human mtDNA and NRY have appeared. Most of these studies have focused on a particular population or region. In some cases, the results of these local studies are easily interpreted in terms of local cultural practices: patrilocal groups show more geographic structure in their Y-chromosomes, while matrilocal groups have more geographically structured mitochondria.[2–4] In other cases, the results reflect known historical events. For example, colonizations consisting primarily of men have resulted in the introgression of European Y-chromosomes—but not mitochondria—into native populations in South America[5,6] and Greenland.[7]

When this type of comparison has been made at the global scale, however, the interpretation is not so clear, and different studies have produced apparently conflicting results. A global survey published in 2004 by Wilder and colleagues found no evidence for a higher female migration rate.[8] These authors attribute the disagreement

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to methodological differences—specifically that previous global results are unreliable due to problems of ascertainment bias.

While we believe that the ascertainment issue is important, these contradictory conclusions draw attention to a deeper issue: the assumptions that typically underlie the analysis of this type of data. It is common to interpret genetic data in terms of models and statistics that implicitly assume equilibrium—that is, that the demographic processes going on today are identical to those that went on in the past. When the population is not at equilibrium, this leads to bias in the analysis and sensitivity to factors that are not generally considered very important, such as the details of the scheme according to which the genetic samples were collected. In the context of sex-biased human migration, equilibrium implies that the relative rates of male and female migration have not changed over time, or that any change occurred so far in the past that it has no influence on the genetic patterns observed today.

The construction of a non-equilibrium model involves the incorporation of many additional possible parameters. In the absence of additional information, it is difficult to determine the best way to parameterize a complex model, and how to constrain it in a way that permits meaningful interpretation of data. In this paper, we address the issue of how to parameterize a simple non-equilibrium model of sex-biased migration, and we make predictions, showing how the departure from equilibrium will affect genetic patterns at the global scale. In particular, patterns in the ethnographic data indicate that the transition to agriculture is associated with an increase in patrilocality. We propose a model in which male and female migration are similar over most of human history, and female-biased migration is a recent phenomenon.

Ancient marital residence patterns

Most human cultures are patrilocal,[9] but this has not necessarily always been the case. Human migration is not an invariant expression of human biology. Cultural norms are important in determining human behaviors, including migration, and these norms can change rapidly. One of the most important cultural changes is the transition from a mobile forager lifestyle to a sedentary agricultural one. This relatively recent transition to agriculture (which began no more than ~10000 years ago in most areas, and much more recently in some) needs to be incorporated into genetic analyses of sex-biased migration.

While it is true that agricultural societies are overwhelmingly patrilocal, the same is not true of non-agricultural societies. Forager societies in the ethnographic record show a more balanced pattern of marital residence than agricultural societies, with matrilocality being nearly as frequent as patrilocality over the whole course of married life.[10] Among foragers, it is common for males to do bride-service and live with their wife's kin in the early years of marriage, after which the couple will live with the husband's kin. Often, couples change their residence from season to season or year to year, residing with the husband's kin at times and the wife's kin at others. This multilocal pattern of residence is especially common among tropical foragers. Furthermore, patterns of residence and dispersal among foragers are quite different from those of sedentary agriculturalists and most other primates. Foragers' camps change location, and individuals move in and out of those camps. The fluidity of forager social groups makes it difficult to say whether males or females are dispersing from their natal area or natal group.

When societies begin to cultivate crops on a particular piece of land, it becomes important to defend that land, and to pass it on to one's children. In humans, like other mammals, male reproductive success can vary much more than female reproductive success. Sons are therefore favored in inheritance of land. Without such a resource, a son may have difficulty in acquiring wives, and may produce no children, whereas a daughter's reproductive opportunities will be less dependent on her inheriting property and wealth. The bias in favor of male inheritance of land means that males tend to live where they were born, while females marry and move elsewhere. Patrilocality is favored even among nomadic pastoralists (~88% of pastoralists), because a male who inherits his father's herds has more success in acquiring wives, and because defending herds is probably best accomplished by keeping related males together.[11] Mobile foragers do not grow crops or accumulate wealth, nor do they control resources like herds, so there is no bias towards male inheritance and patrilocality among these societies.

It is common to take forager populations as a model for pre-agricultural human societies. The residence patterns of mobile foragers suggest that human patrilocality may not be an ancient phenomenon, but rather that the majority of human history was characterized by similar male and female migration rates, or possibly even male-biased dispersal.[12] At least one analysis of non-human primates also argues against ancient patrilocality (or male philopatry): a comparison of modern ape species indicated that the last common ancestor of gorillas, chimps and humans is likely to have had male-biased dispersal.[13]

The effect of the difference in marital residence between foragers and agriculturalists has been noted in the genetic data. Early genetic studies of aboriginal forager (!Kung and pygmy) populations in Africa revealed more geographic structure in the mtDNA than in autosomes, in contrast with what was seen among agricultural (Bantu, European, and East Asian) populations.[12] More recently, comparison of patterns of mtDNA and NRY variation in sub-saharan African forager and agricultural populations found that the genetic evidence for patrilocality was significantly stronger among the agriculturalists.[4,57]

The spread of agriculture is likely to have been associated with a reduction in male migration, and possibly also an increase in female migration. Just as the cultural and

geographic variation in marital residence practices can be seen in the genetic data, we expect that the historical transition to agriculture, and the associated increase in patrilocality, will also have left a genetic mark, and that this mark may be discernible in global patterns of human genetic diversity.

The importance of real geography

Most analyses attempting to compare male and female demographies have not considered geographically explicit models. Calculations based simply on F_{ST} are implicitly using a non-geographic, island model of population structure (Box 1). Models of isolation by distance (Box 2) incorporate a more realistic notion of geography. The reliance on simple analyses assumes that a more geographically explicit analysis would not significantly alter the main conclusions. For populations at equilibrium, this assumption is often correct. Using an island-model formula to analyze isolation-by-distance data introduces significant biases, but will not affect inference of the *relative* male and female migration rates, since the biases in the mtDNA and NRY analyses cancel out.[14]

However, if the relative rates of male and female migration have changed over time, explicit consideration of geography is indispensable. A change in migration will alter patterns of genetic diversity, but the effect on genetic diversity takes time to develop. Exactly how much time depends on the geographic size of the region being studied, and on the details of how sampling locations are distributed. Inferences about human history are known to be sensitive to the sampling strategy. For example, the frequency of rare alleles observed in human genetic data increases with the number of populations or ethnicities sampled.[15,16] In this paper, we show another important effect of sampling that arises in a non-equilibrium context. Specifically, genetic patterns within a particular region reflect only the recent history of that region. By contrast, genetic patterns at larger geographic scales reflect more ancient demographic processes.

Local genetic patterns represent recent demographic history

Recent work in coalescent theory has shown that, in models of geographic structure, the long-term coalescent behavior (the expected shape of the genealogical trees in the distant past) is nearly independent of the details of the sampling scheme.[17,18] In models of isolation by distance, the deeper (older) portions of the genealogy consist of lineages that will have traversed the habitat multiple times.[19,20] This means that the information about geographic structure contained in genealogies is largely limited to the most recent portions of those genealogies—the tips of the trees. In fact, this recent, informative portion of genealogies typically represents a very small proportion of the overall genealogy depth.[21]

A corollary of this observation is that statistics like F_{ST} will be determined predominantly by demographic patterns in the recent past. This means that changes in migration that occurred in the distant past will not be detectable in current genetic patterns, even if those changes occurred more recently relative to the most recent common ancestor of the population. For very recent migration change, the expected value of F_{ST} will be influenced by both the old and new rates. The more recent the change, the more important the old rate will be. Under the island model, all that is expected is this gradual replacement of one genetic pattern by another.

Under models of isolation by distance, more complex patterns develop during the transition following a change in migration. As in the island model, a new genetic pattern gradually replaces the old. However, in a geographically explicit model, this replacement occurs at different rates, depending on geographic scale. The degree of genetic differentiation between two sampling sites depends on the time since the migration change and the distance between the sites. Intuitively, the new migration rate will not dominate the data until enough time has passed for migrants to have traveled between the two sites. The farther apart the sites are, the longer this will take. This distance dependence implies that inferences based on local-scale sampling will apply only to the most recent history, whereas widely separated samples may be able to retrieve older migration patterns.

This sensitivity of genetic patterns to recent demography is evident in patterns of mtDNA and NRY diversity in two sets of populations among the hill tribes of northern Thailand.[2] Three matrilocal groups studied showed a trend towards high within-group NRY diversity (high male migration) and high between-group mtDNA divergence (low female migration). Three patrilocal groups showed the opposite pattern of variation. A more detailed and quantitative reanalysis of the same data has revealed a correlation between the genetically inferred rates of migration and ethnographically observed degrees of rigidity of marital residence (strict patrilocality versus a less rigid matrilocality).[3]

All six groups are from the same geographic region and speak closely related Tibeto-Burman languages. The matrilocal groups include the Lahu, Red Karen, and White Karen; the patrilocal groups include the Akha and two groups of Lisu. The relationship among the languages spoken by these six groups is illustrated in Fig. 1.[22] One of the matrilocal groups (the Lahu) lies within the linguistic clade of the three patrilocal groups. Furthermore, divergence of all of the $>$250 Tibeto-Burman languages is thought to have occurred within the past 4000 years.[23]

The degree of linguistic similarity and interrelatedness suggests that differences in marital residence are unlikely to represent an ancient cultural divergence between these two sets of populations. Rather, this genetic data illustrates how local patterns of genetic diversity respond to cultural changes over a relatively small number of generations.

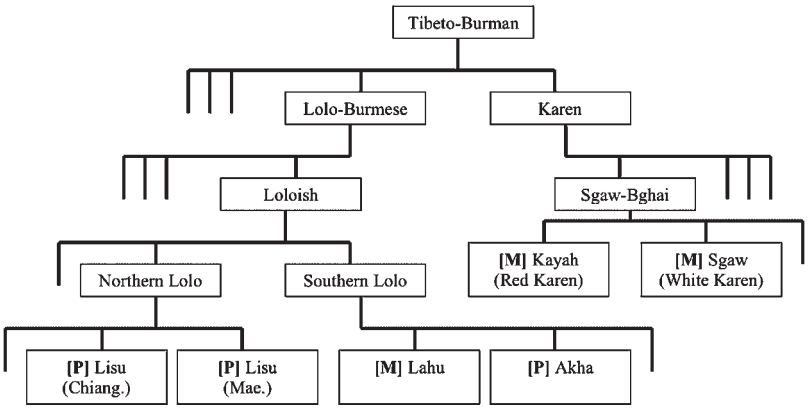

Figure 1. Linguistic relationships among the hill tribes of Northern Thailand. This partial language tree is based on linguistic relationships described in the Ethnologue.[22] One of the three matrilocal groups speaks a language that is more closely related to the languages of the three patrilocal groups than to those of the other matrilocal groups. The Tibeto-Burman language family consists of at least 250 contemporary languages, which are thought to have diverged from a common Tibeto-Burman ancestor within the last 4000 years. Note that only one or two of many language subfamilies are represented at each node.

Spread of the new genetic signature following a migration change

In a model where the habitat is continuous, it is common to describe the migration rate in terms of a dispersal variance, σ^2. For example, if we take a mtDNA sample from a woman born at a particular location, these models describe the birthplace of the woman's mother as a bivariate normal (Gaussian) distribution centered on the sampled woman's birthplace, with a variance of σ^2 in each direction. The term σ has units of distance, and can be thought of as the "typical" distance between the birthplaces of a parent and its offspring. We are interested in describing the effect of a change in this migration rate at a time τ generations in the past. We indicate the old migration rate (more than τ generation in the past) as σ_1, and the new migration rate (for the most recent τ generations) as σ_2.

We have simulated the coalescent process in a two-dimensional, continuous habitat. The details of this simulation process have been described elsewhere.[21] The habitat is a rectangle of dimension 10×20 (in arbitrary units) with a population of uniform density and total haploid size 200,000. The mean coalescence time (in generations) for a pair of adjacent samples is t_0, and for a pair of samples separated by a distance x it is t_x. Under equilibrium conditions ($\sigma_1 = \sigma_2$), and ignoring boundary effects, the ratio $(t_x\text{-}t_0)/t_0$ ($=F_{ST}/(1\text{-}F_{ST})$) is expected to increase linearly with Log(x), with a slope that depends on σ^{24}—the higher the value of σ, the shallower the expected slope.

For given values of σ and τ, there is a characteristic distance x^* defined by diffusion under the new migration scheme: $x^* \approx \sqrt{2\sigma_2^2\tau}$. For sampling locations separated by a distance of less than x^*, the new migration rate σ_2 will dominate the genetic patterns, while differentiation at distances greater than x^* will depend more on the old migration rate. A process similar to this has been described for a slightly different non-equilibrium model. Following a rapid range expansion, isolation by distance appears gradually, and is evident first over short distances, and spreads at a similar rate.[25]

We simulated four migration scenarios. Two equilibrium scenarios assume a migration rate that was constant through time, with σ equal to either 0.05 or 0.15. The other scenarios feature a reduction in the migration rate. In these non-equilibrium simulations, we set the old dispersal rate, σ_1 to 0.15, and the new dispersal rate, σ_2 to 0.05. The transition from the old rate to the new one occurred either $\tau = 40$ or $\tau = 400$ generations in the past. Fig. 2 plots the average estimated value of $F_{ST}/(1\text{-}F_{ST})$ against as a function of the logarithm of the distance between sampling sites. For the two equilibrium simulations, the simulated values (open and closed circles) are similar to the expected values (solid lines) based on Rousset's analysis. For the two non-equilibrium simulations, we have calculated the critical distance x^*, indicated by the two vertical, dashed lines. At distances shorter than x^* the average estimated $F_{ST}/(1\text{-}F_{ST})$ increases with distance at the rate expected under the recent migration rate, σ_2. At distances greater than x^*, this estimated value increases more slowly, at the rate expected under the old migration rate, σ_1.

Is this relevant to human demographic history?

The effect that we are describing is relevant to human genetic data only if the transition to patrilocality occurred sufficiently recently for the older migration patterns still to be evident at some geographic scales. If we date the transition at ~10000 years before present and take the average human generation

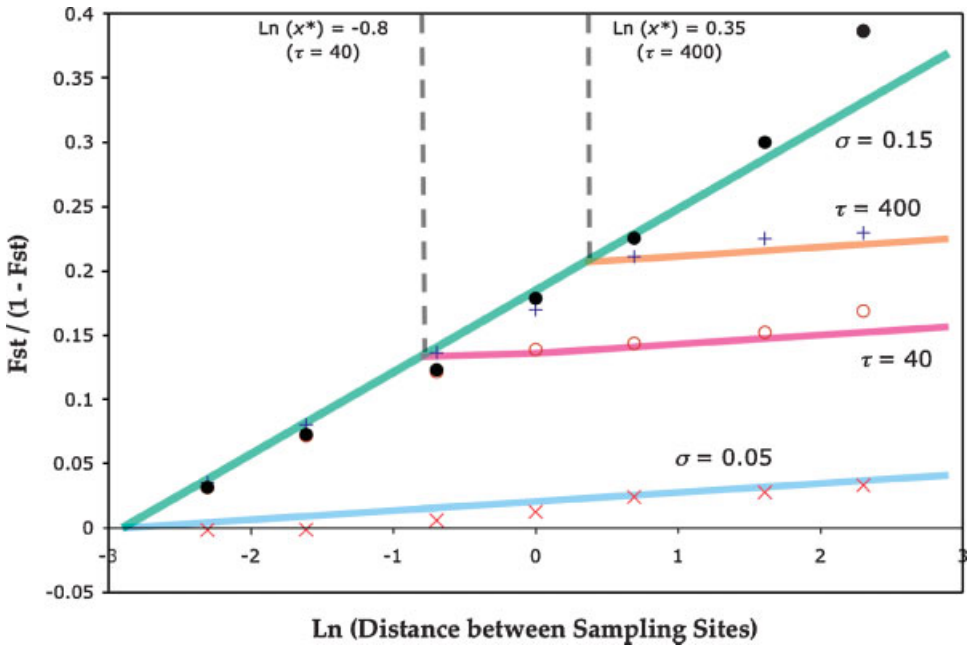

Figure 2. Spread of the genetic consequences of a change in migration. This graph illustrates how the pattern of isolation by distance changes under non-equilibrium migration. Under equilibrium migration (constant migration rate), the expected value of $F_{ST}/(1\text{-}F_{ST})$ between a pair of sites increases linearly with the natural logarithm of the distance between those sites. The slope is equal to $1/Nb$, where Nb is the neighborhood size. The blue line has the expected slope for $\sigma = 0.15$ (slope = 0.00707). The red crosses represent the mean estimated values of $F_{ST}/(1\text{-}F_{ST})$ based on coalescent simulations with this migration rate. The green line and filled circles represent the corresponding expected and observed (simulated) values for $\sigma = 0.05$ (slope = 0.06366). Under non-equilibrium migration, where $\sigma_2 = 0.05$ in the recent past and $\sigma_1 = 0.15$ in the distant past, the slope of $F_{ST}/(1\text{-}F_{ST})$ versus ln(distance) depends on the distance and τ, the time since the change in migration. At distances less than $x^* \approx \sqrt{2\sigma_2^2\tau}$, the slope is determined by σ_2, while the slope at greater distances is determined by σ_1. The open circles and vertical crosses represent simulation results for $\tau = 40$ and 400 generations, respectively. The corresponding values of x^* are indicated by the vertical dashed lines. These values follow the steep green line (corresponding to $\sigma_2 = 0.05$) at distances less than x^*. At longer distances, the expected slope is indicated with the pink ($\tau = 40$) and orange ($\tau = 400$) lines. Note that these lines are parallel to the blue line corresponding to the old migration rate $\sigma_1 = 0.15$.

time to be 25 years, this corresponds to ~400 generations ($\tau = 400$).

The critical distance associated with this time is proportional to the typical migration distance: $x^* \approx \sqrt{2\sigma_2^2\tau} \approx 28\sigma_2$. Eurasia is on the order of 10000 km long from east to west. In order for the pre-agricultural genetic patterns to have been fully replaced at this geographic scale, the typical migration distance σ_2 would need to have been on the order of 360 km per generation. Marital distance (the distance between the birthplaces of a husband and wife) in small-scale societies typically averages less than 100 km, with a mean of around 40 km in forager societies, and less among horticulturalists.[26] If typical human dispersal has been closer to 30 km per generation, we should expect to see evidence of pre-agricultural migration patterns at distances of over 1000 km.

The transition to agriculture occurred at different times in different regions, and for some populations has never occurred. There are two obvious ways in which this asynchronous transition might bias our critical-distance estimate. On one hand, the fact that agriculture arose more recently than 10000 years ago in most locations suggests that this estimate is too large. On the other hand, the fact that agricultural societies tend to expand and often displace their non-agricultural neighbors should increase the rate at which the post-agricultural patterns spread. This heterogeneity could only be fully accommodated in a complex and geographically detailed model, but this estimate at least suggests that the genetic vestiges of our pre-agricultural, multi-local ancestry may still be identifiable at the largest geographic scales.

F_{ST} under different sampling schemes

One consequence of a recent migration change in a model of isolation by distance is that the behavior of summary statistics such as F_{ST} will depend on the geographic scale over which samples are taken. To illustrate this effect, we have simulated datasets under a non-equilibrium migration model similar to the one proposed here. Datasets were simulated for two loci (mtDNA and NRY) collected using three different sampling

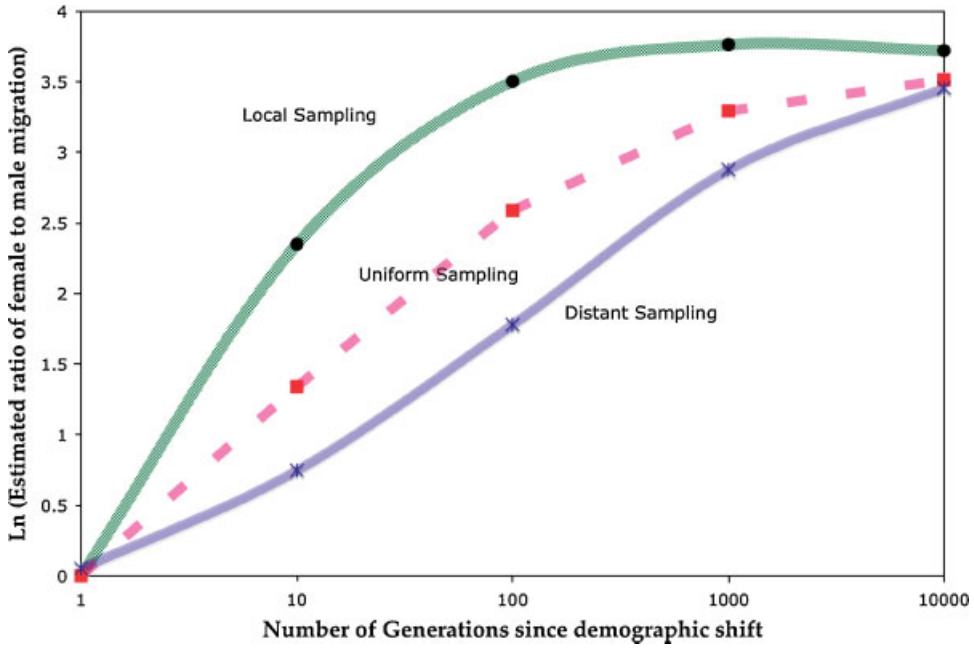

Figure 3. The effect of sampling distribution on comparisons of FST under a non-equilibrium model of migration. **A:** illustrates the three sampling schemes used in simulations whose results are presented in **B**. The filled diamonds represent the "local" sampling scheme, the twenty-five crosses represent the "uniform" sampling scheme, and the four open diamonds represent the "distant" sampling scheme. Simulations assumed a sample of size ten from each site. The specific sampling locations for each lineage were drawn at random from an area around the site corresponding to regional population of twenty. F_{ST} values were estimated by comparing the mean number of pairwise differences among all pairs of samples and the mean number of differences from all pairs from the same site. The ratio of male to female migration was estimated assuming an equilibrium island model. Ten thousand datasets were simulated for each value of τ, the time at which the migration pattern changed. The mean estimated ratio of male to female migration is plotted on a log-log scale in **B**. **B:** illustrates the effect on estimates of sex-biased migration of a change in migration at time τ generations in the past. Prior to τ generations in the past, migration is assumed to be equal for males and females ($\sigma_{mtDNA} = \sigma_{NRY} = 0.15$). For the most recent τ generations, migration is strongly female biased ($\sigma_{NRY} = 0.03$; $\sigma_{mtDNA} = 0.3$). For changes in the very distant past (large τ), the genetic patterns have nearly equilibrated under the new migration pattern, and F_{ST} values represent this new pattern ($F_{ST\ (male)} > F_{ST\ (female)}$; $\sigma_{NRY} > \sigma_{mtDNA}$) at all sampling scales. At smaller values of τ, however, the population is not at equilibrium, and the relative migration rate inferred from mtDNA and NRY F_{ST} estimates depends strongly on the geographic scale over which samples were collected. Local sampling (green line, filled circles) responds most quickly to the change in migration. The uniform sampling scheme (red dashed line, filled squares) responds more slowly. The distant sampling scheme (purple line, stars) responds most slowly, so that patterns observed at this scale are most reflective of the old migration scheme.

schemes (Fig. 3). For the most recent τ generations, the loci have different dispersal rates: $\sigma_{mt2} = 0.3$ and $\sigma_{Y2} = 0.03$. Prior to τ generations in the past, both loci have the same dispersal rate ($\sigma_{mt1} = \sigma_{y1} = 0.15$). An infinite sites model of mutation with $\mu = 0.001$ per locus per generation was assumed. The three sampling schemes are illustrated in Fig. 3A.

We estimated F_{ST} for each simulated mtDNA and NRY dataset. We then calculated the ratio of female to male migration that would be inferred from that data under an island model at equilibrium. The average inferred ratio for each of the three schemes is plotted in Fig. 3B as a function of τ, the time since the transition. For a change that occurred sufficiently far in the past ($\tau \geq 10000$), the inferred sex bias in migration is similar under each of the three sampling schemes. For more recent changes (smaller values of τ), both the old and new migration patterns influence estimated F_{ST} values. In this transitional period, the recent migration history predominates when sampling is done on a local scale, whereas ancient migration patterns are more evident among geographically distant samples.

The studies

The sampling schemes used for the simulations presented in Fig. 3 were chosen by rough analogy with the three studies discussed here in detail. The local sampling scheme, chosen by analogy to the Thai hill tribes studies[2,3] is most sensitive to the recent migration history of the population. The other two sampling schemes were chosen to illustrate the effects on global patterns. The dense, global sampling scheme, analogous to the Seielstad study[1] is more sensitive to recent

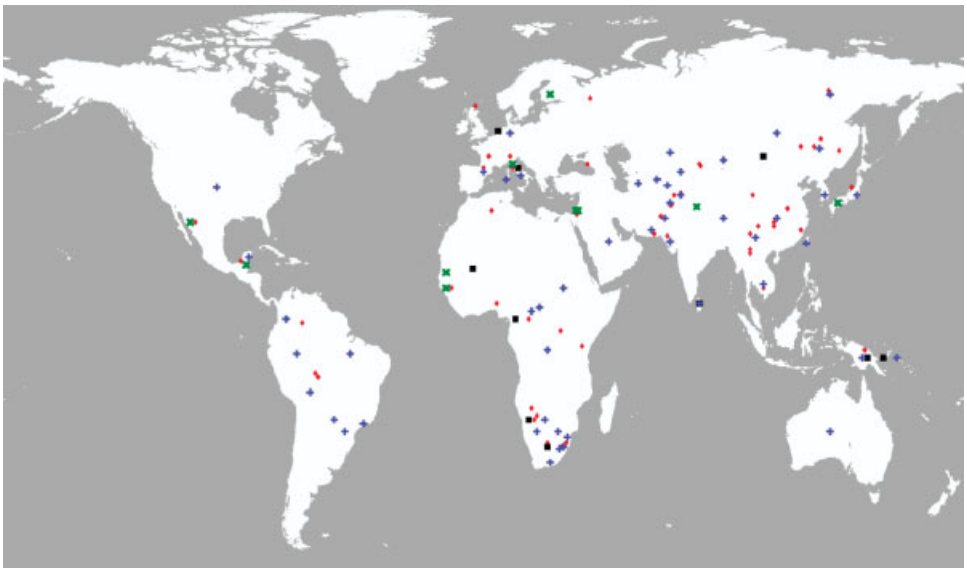

Figure 4. The distribution of samples in global studies. The approximate distribution of sampling locations of the studies by Seielstad[1] and Wilder[8] are illustrated here. Sampling of the mtDNA and NRY data analyzed by Seielstad is indicated by diagonal green and vertical blue crosses, respectively. The sampling locations used by Wilder are indicated by solid black squares. For comparison, the sampling distribution of the Human Genome Diversity Cell Line Panel[29] are indicated by the red diamonds.

migration patterns than is the geographically sparse scheme, analogous to the Wilder study.[8] We suggest that a part of the explanation for the different conclusions reached in these two studies stems from the difference in sampling schemes. The denser set of samples used by Seielstad may be more reflective of post-agricultural, patrilocal marital residence patterns, whereas the sparser sampling scheme of Wilder may be accessing the older, multilocal migration patterns of our forager ancestors. These sampling schemes are illustrated in Fig. 4.

Multi-locus genetics

A major limitation common to all studies focusing solely on mtDNA and NRY markers is stochastic variability. Because these molecules are large and non-recombining, it is possible to reconstruct detailed genealogies for each of them. However, any single genealogy is typically consistent with a wide range of possible underlying demographic histories. Distinguishing among those possible histories requires statistical power available only from multi-locus data.[27] For example, Wall has estimated that 50–100 loci will be required to determine whether archaic human populations (e.g. Neanderthals) contributed to the modern human gene pool.[28]

Human population genetics is being transformed by our access to unprecedented quantities of data, and it will soon be common to base human genetic analyses on global, multi-locus datasets. Multi-locus data derived from the HGDP-CEPH Human Genome Diversity Cell Line Panel (HGDCLP)[29] have been used to study human population structure.[30,31] Similar analyses have been performed on populations of the bacterium *Helicobacter pylori*, which colonizes the human stomach lining. Due to *H. pylori*'s low rate of transmission and high rates of recombination and mutation, these data provide information that complements the results from human genetic data.[32–34]

The growing availability of multi-locus data may also be useful for studying sex differences in migration. An autosomal allele is present in males and females with equal frequency, and therefore experiences an average of the male and female migration rates. In 2000, Jorde and colleagues published a study comparing mtDNA and NRY data with autosomal markers.[35] These authors interpret their results as being broadly consistent with the results of the Seielstad study.

The Jorde study considers the global patterns in more detail, however, and raises questions about heterogeneities among different geographic regions. Microsatellite diversity on the NRY is markedly reduced in two European populations (northern Europeans and Finns), which also show extremely high levels of divergence from other European populations. This pattern suggests a relatively recent regional bottleneck, possibly associated with migration into the region or regional selection. These results point to the importance of using models that permit geographic variation in demographic parameters, in addition to the type of temporal variation that we have focused on here.

The other promising source of multi-locus data for studying sex-biased migration is the X chromosome. An X-linked allele is found in a female twice as often as in a male, and its effective migration rate is a weighted average of male (1/3) and female (2/3) migration. The different inheritance patterns of X-linked and autosomal loci mean that sex differences in demography will produce differences in the patterns of autosomal and X-chromosome diversity. Studies using X-linked loci to study human history have recently been reviewed by Schaffner.[36]

Two of these studies have compared X-linked and autosomal patterns of diversity in global samples. Wilson and colleagues[37] used the program STRUCTURE[38] to assign 354 individuals to genetic clusters on the basis of 23 X-linked or 23 autosomal microsatellite loci. They found better correlation of this assignment with geographic origin for autosomes than for X-linked loci, and suggested that this might reflect a higher female migration rate. By contrast, when Ramachandran and colleagues[31] performed a similar analysis on 20 of each type of locus for 1056 individuals, they found no significant difference in the ability to identify geographic clusters, suggesting an absence of evidence for large differences between male and female demographic parameters (such as migration).

The apparent contradiction between these two studies is reminiscent of the conflicting conclusions of Seielstad and Wilder. As with those studies, the Wilson and Ramachandran studies are based on different geographic sampling schemes. However, the schemes are not qualitatively different in the way that the schemes of Seielstad and Wilder are, and an analogous attempt to reconcile these results would require the construction of a much more geographically and historically explicit model. There is also the question of which among these results, if any, need to be reconciled. That is, when is it likely that differing results simply reflect stochastic variation, and when is it likely that they represent real differences that need to be accounted for? We believe that it is worthwhile to consider briefly how robust comparisons of X-linked and autosomal markers are to this variation. In particular, how does this compare to the robustness of a comparison of mtDNA and NRY markers?

How much power is in an X versus autosome comparison?

Because the X-chromosomes and autosomes both average over male and female histories, any single X versus autosome (X/A) comparison has less discriminatory power than the mtDNA versus NRY (mt/Y) comparison. However, this limitation may be outweighed by the additional power that comes from using multiple loci. This tradeoff raises the question of just how much is gained by using multi-locus data. For the specific case of sex-biased migration, we can do a rough calculation of the relative power of X/A and mt/Y comparisons. Suppose that the real male and female migration rates are m_m and m_f, respectively, and that NRY and mtDNA analyses produce unbiased estimates of these migration rates. If we assume that the variance associated with each of these estimates is the same ($s_{mt}^2 = s_y^2 = s_{mt/Y}^2$), the power to detect a migration difference will be determined roughly by this signal-to-noise ratio:

$$\frac{|m_f - m_m|}{s_{mt} + s_Y} = \frac{0.5|m_f - m_m|}{s_{mt/Y}}. \quad (1)$$

Analysis of an autosomal locus estimates $(m_m + m_f)/2$, while an X-linked locus estimates $(m_m + 2m_f)/3$. Assume the variance of each of these estimates is ($s_x^2 = s_A^2 = s_{X/A}^2$), so that the variance of the estimate from n independent loci is approximately $s_{X/A}^2/n$. The corresponding power of an X/A comparison is then:

$$\frac{|m_f - m_m|/6}{\frac{s_X}{\sqrt{n_X}} + \frac{s_A}{\sqrt{n_A}}}. \quad (2)$$

For example, the full study by Ramachandran,[31] analyzed 20 X-linked and 377 autosomal microsatellite loci ($n_X = 20$, $n_A = 377$). For this study, equation 2 reduces to:

$$\frac{0.6|m_f - m_m|}{s_{X/A}}. \quad (3)$$

This means that this X/A comparison would be roughly 20 percent more powerful than a traditional mt/Y comparison, if each individual locus were equally informative (if $s_{mt/Y} = s_{X/A}$)—that is, 20 percent better than a comparison of a single mtDNA microsatellite with a single Y-chromosome microsatellite. In practice, mtDNA and NRY genetic data will be significantly more informative than a single microsatellite ($s_{X/A} \gg s_{mt/Y}$).

For the subanalyses by Wilson[37] and Ramachandran[31] comparing equal numbers of X-linked and autosomal microsatellites (23 for Wilson and 20 for Ramachandran), the power of this comparison is even less than for a single mt/Y microsatellite comparison:

$$\frac{0.4|m_f - m_m|}{s_{X/A}} \text{ for 23 loci, or } \frac{0.37|m_f - m_m|}{s_{X/A}} \text{ for 20 loci.} \quad (4)$$

Studies like this will become more powerful as the number of loci—particularly the number of X-linked loci—incorporated into analyses increases. The X-chromosome is a potential source of hundreds of informative loci, so it is only a matter of time before these comparisons begin to outperform the mt/Y comparison. However, at present, mt/Y studies represent a more reliable source of information on sex differences than X/A studies. Despite their use of multi-locus data, the conflicting results of Wilson and Ramachandran are actually more likely to reflect stochastic variation than are the conflicting results of Seielstad and Wilder. The major caveat regarding this calculation is the assumption that estimates based on the mtDNA and NRY are unbiased. Because these two chromosomes contain multiple linked genes, they may have been more strongly shaped by selection than the X-linked and

Box 1: Geographic structure and F_{ST}

Geographic patterns of genetic diversity are shaped, in part, by the demographic history of the population: the population's size and range, as well as its patterns of reproduction and migration over time. Intuitively, we expect two individuals sampled from nearby locations to be genetically more similar to each other than individuals sampled from two geographically distant locations. When migration rates are high, populations are genetically well mixed, and the correlation between genetic distance and geographic distance is modest. When migration rates are low, local genetic drift results in the accumulation of genetic differences between different regions.

The formalization of this intuition into quantitative models has a long history in population genetics. The most commonly used statistics in assessing geographic structure from genetic data are estimators of F_{ST}. The "F-statistics" were originally developed by Sewall Wright to describe the reduction in heterozygosity resulting from inbreeding.[41] In the context of structured populations, F_{ST} is a measure of how genetically similar samples drawn from the same location are, compared with the genetic diversity of the population as a whole. Low F_{ST} values (close to zero) indicate a relatively homogeneous population, while high F_{ST} values (approaching one) indicate strong genetic divergence among subgroups.

In recent decades, population geneticists have tended to think of F_{ST} in slightly different terms. These inbreeding coefficients have been related to more contemporary concepts in population genetics, such as the average time to the most recent common ancestor of a pair of alleles at a locus.[42] A number of estimators of F_{ST} have been developed.[43–46] These differ in their details, but the basic principle is to compare genetic diversity within demes to genetic diversity between demes, or within the population as a whole. An appealing feature of these statistics is that they are based on a ratio of measures of diversity, and therefore do not depend on the mutation rate (at least in the limit where the mutation rate is small).

The quantity most famously associated with F_{ST} is $1/(1+4Nm)$, where N is the size of each subpopulation, or deme, and m is the per-generation probability of migration.[47–49] This is the expected value of F_{ST} for autosomes in a diploid population at equilibrium under the symmetric island model of population subdivision.[48,50] For the NRY and mtDNA, the expected values of F_{ST} depends on the male and female effective population sizes and migration rates, respectively: $E[F_{ST\ (NRY)}] = 1/(1+2N_m m_m)$; $E[F_{ST\ (mtDNA)}] = 1/(1+2N_f m_f)$. Assuming equal effective population sizes for males and females ($N_m = N_f$), these equations produced the original estimate of eight-fold higher female migration.[1]

autosomal microsatellites, in which case, the X/A comparison, while less powerful, would more accurately reflect the purely demographic aspects of human history.

Effective population size

The other demographic parameter that we have mentioned at several points, but not considered explicitly, is the effective population size. Standard population genetic methods do not provide a direct estimate of migration, but rather an estimate of the product of the migration rate m and the effective population size Ne (see Box 1). The original estimate by Seielstad relied on the argument that the male and female effective population sizes are unlikely to be dramatically different in humans.

Box 2: Isolation by distance

Under the assumptions of the island model, a migrant entering one subpopulation, or *deme*, is equally likely to have come from any of the other demes. In some sense, this is a model of population structure without geography. In many circumstances, we expect that migrants will derive preferentially from nearby demes. In this case, the expected genetic divergence between subgroups will increase with the geographic distance between them, a phenomenon known as isolation by distance.[51,52] The theory of isolation by distance has been developed both in the context of continuous populations and the "stepping-stone" model of population structure.[53–56]

Methods have also developed to estimate dispersal from pairwise F_{ST} estimates.[24,25] In these methods, F_{ST} (or some function of F_{ST}) is estimated for each pair of locations where samples were collected. The rate at which this scaled genetic divergence increases with the distance between the two locations is used to estimate the rate of gene flow. For instance, in the method of Rousset,[24] the quantity $F_{ST}/(1\text{-}F_{ST})$ for each pair of sites is plotted against either the distance between those sites (in one dimension), or the logarithm of the distance between sites (in two dimensions). The reciprocal of the resulting slope provides an estimator of the *neighborhood size* ($4\pi\sigma^2\rho$, where ρ is the population density, and σ^2 is the variance of dispersal profile). Roughly speaking, this is the number of individuals within the range of a single generation of migration.

The simulation results presented here also assume equal male and female effective population sizes, and focus on chromosomes with the same nominal value of Ne under this assumption. The larger effective population sizes of X-linked and autosomal loci suggest that these genes might reflect older demographic processes than the mtDNA and NRY, although we have not explicitly modeled that effect here. A more-thorough analysis would also incorporate the possibility of different male and female values of *Ne*, and that the magnitude of this difference may have varied over time like the ratio of migration rates. The higher variance of male reproductive success is expected to translate into a reduced male effective population size. If cultural transitions, like the adoption of agriculture, are systematically associated with a change in the distribution of reproductive success, this effect could produce changes similar to those described here for a change in the migration rate. The genetic consequences of a change in *Ne* would propagate spatially in a manner similar to the propagation illustrated in Figs. 2 and 3 for a change in migration.

Some recent studies have attempted to compare the value of *Ne* for males and females. In a paper published around the same time as their study of male and female migration, Wilder and colleagues provided evidence that *Ne* is systematically greater for females than for males.[39] The Ramachandran study comparing X-linked and autosomal markers actually found evidence for *Ne* being lower for females than for males. Comparison of these results is difficult because the analytic methods are so different. The Wilder study used coalescent simulations to examine a number of bottleneck and selective sweep scenarios, whereas the Ramachandran study focused on a model of divergence with constant effective population size. A recent paper attempting to incorporate cultural change in this context argues that NRY patterns suggest a recent increase in *Ne* for males, possibly reflecting a shift from polygyny to monogamy.[40] As in the case of migration, we believe that explicit consideration of this type of cultural change is an indispensable part of studies of human genetics, and that basing analyses on more realistic models may help to resolve apparent discrepancies among different studies.

Conclusion

Humans are unusual in that many of the demographic factors shaping our genetic diversity (e.g. patterns of migration and reproduction) depend strongly on cultural practices. These practices can change on a timescale that is short relative to depth of human gene trees. One challenge facing researchers in this area is how to incorporate some of the complexities that we know are important to human history, but without introducing so many parameters that the models over-fit the data or become uninterpretable. For the specific case of human migration, we have shown how knowledge from other fields can be used to sensibly construct a more realistic method for analyzing human genetic data. Patterns in the ethnographic record identify the adoption of agriculture as a major transition point for sex differences in human migration.

In order to make the best use of the emerging wealth of genetic data, methods of analysis need to be developed that are robust to the complexities of human demographic history. We have discussed just one of many cultural phenomena that are likely to have influenced patterns of human genetic diversity. Consideration of at least some non-equilibrium demographic processes will likely be required for us to meaningfully interpret data. This will require the development of new models and analytic tools as well as a continued dialogue between human molecular genetics and the social sciences, whose observations can inform more sophisticated analyses of human genetic data.

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