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The Human Genetic History of the Americas: The Final Frontier

Review

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The Americas, the last continents to be entered by modern humans, were colonized during the late Pleistocene via a land bridge across what is now the Bering strait. However, the timing and nature of the initial colonization events remain contentious. The Asian origin of the earliest Americans has been amply established by numerous classical marker studies of the mid-twentieth century. More recently, mtDNA sequences, Y-chromosome and autosomal marker studies have provided a higher level of resolution in confirming the Asian origin of indigenous Americans and provided more precise time estimates for the emergence of Native Americans. But these data raise many additional questions regarding source populations, number and size of colonizing groups and the points of entry to the Americas. Rapidly accumulating molecular data from populations throughout the Americas, increased use of demographic models to test alternative colonization scenarios, and evaluation of the concordance of archaeological, paleoenvironmental and genetic data provide optimism for a fuller understanding of the initial colonization of the Americas.

Introduction

In 1590, barely a century after European arrival in the Americas, Friar José de Acosta [1] argued that the native inhabitants of the Americas must derive from populations of Asia. He further speculated that the transit from Asia was unlikely to have been by water, but rather overland via some as yet undiscovered connection between extreme northwest North America and northeast Asia — thus anticipating the Beringian migration hypothesis by several centuries.

Throughout the 20th century, indigenous populations from the North American arctic to the southern cone of South America were characterized genetically for a suite of classical markers [2,3], such as blood group, serum protein and enzyme polymorphisms, which confirmed the Asian origin of Native American populations. These early studies demonstrated that marker frequencies were geographically structured throughout the Americas, and led to the proposal of several alternative hypotheses regarding number, routes and timing of the original migrations to the Americas. However, the evolutionary and historical resolution of these classical markers, mostly biallelic systems, was coarse.

These genetic studies were motivated by archaeological research that provided the early outline of Native American origins. By the mid-20th century, it was clear that Beringia constituted the land connection between Asia and North America during the last glacial maximum (LGM) around 20 thousand years ago (kya). In addition, the identification of the Clovis culture — a 13 thousand year old stone tool tradition found in sites across North America — as the earliest and most widely distributed archaeological tradition in North America made it a candidate for the tool-kit carried by the earliest American migrants (Box 1). Martin's [4] hypothesis of a rapidly moving and expanding population of Clovis hunters crossing Beringia and dispersing into the interior of North America through an ice-free corridor between receding glacial masses (the '*blitzkrieg*' model of American colonization) seemed supported by then-available data. The general attribution of American colonization to a trans-Beringian migration led Greenberg *et al.* [5] to propose a model combining linguistic, archaeological, and biological evidence. Their 'Three Wave' migration hypothesis divided all Native Americans into three language groups (Amerind, Na-Dene, and Eskimo-Aleut), which were hypothesized to have entered the Americas sequentially after the LGM, coincident with the first appearance of the Clovis culture. More recent archaeological work, however, has raised significant questions regarding the adequacy of this long-held view of American colonization.

Perhaps the most startling discovery is that the earliest occupation sites in the Americas have been found in South America rather than North America — unexpected if colonization proceeded from North to South. Additionally, recent archaeological work in Siberia suggests there was no significant human presence in northeast Siberia during the LGM [6] to serve as a source population for a rapid, post-LGM colonization. Moreover, the highest concentration of Clovis artifacts is found in eastern North America. If artifact concentration is indicative of population density, then the highest population density in North America immediately following the LGM is on the Atlantic coast rather than in the interior of the continent as would be expected under the traditional 'blitzkrieg' model of American colonization. Thus, the archaeological data in the Americas continue to raise questions regarding the timing and mode of colonization. The resolution afforded by the newer molecular data assists in evaluating alternative migration scenarios.

The Genetic Evidence

Mitochondrial DNA

The majority of molecular genetic studies of Native American populations have utilized the maternally inherited mitochondrial genome. Early research on mitochondrial diversity identified five major haplogroups (A, B, C, D and X) present in indigenous American populations through restriction fragment length polymorphisms, a 9-base deletion, and direct sequencing of the first hypervariable segment of the non-coding D-loop (HVSI) [7–9]. With recent refinements in molecular methods, there has been an increasing emphasis on the analysis of entire mitochondrial genomes [10–14], facilitating the identification of numerous sub-lineages (Table 1). Similar diversity values have been found for all haplogroups, with a number of exclusively American polymorphisms indicative of a signature of recent population expansion [11]. Nonetheless, the number of haplogroups found in Native America is but a subset of those commonly

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Box 1

The Clovis culture.

The Clovis archaeological culture is the earliest, broadly distributed archaeological tradition in North America. The most distinguishing feature of this stone tool kit is the large, bifacially flaked and fluted projectile point. Originally found in association with large mammal (Mammoth) remains, the conventional view of Clovis hunters was that of highly mobile large game specialists who colonized the Americas as they followed herds of large mammals south after the last glacial maximum. The early suggestion that this reliance of Clovis hunters on large herbivores resulted in the extinction of many taxa immediately following the Last Glacial Maximum (LGM) remains highly controversial [46]. Geographically, Clovis sites and artefacts have been found between the southern glacial margin of the LGM to Central America. Clovis sites are not known in South America. Despite its early discovery in the western US, the highest concentration of classic Clovis artefacts is seen in eastern North America.

It is now clear that the classic Clovis point was but one of many tool types used by early PaleoIndian populations, that they relied on many resources besides large game, and they were temporally restricted. The Clovis culture most likely existed for only a short period of time (around 13,000 ± 200 years before present) [47]. A number of sites in both North and South America pre-date Clovis sites, indicating that Clovis hunters were not the earliest migrants to the Western Hemisphere (relevant sites reviewed in [15]). It seems increasingly probable that Clovis represents an expansion of a successful cultural adaptation that developed among earlier colonists south of the North American ice limit of the LGM. Whether this expansion also included a significant movement and migration of the bearers of Clovis culture, or was solely a case of cultural diffusion, is open to question.

found in central and northeast Asia, clearly reflecting a reduction in mtDNA diversity in the Americas.

The question of the timing of colonization is of crucial importance, yet there is considerable variation in mitochondrial haplogroup coalescence estimates. A commonly cited age of Native American mtDNA haplogroups is between 20 and 15 kya, with a possible subsequent expansion giving rise to circum-Arctic populations [15]. Other estimates suggest an earlier origin and migration between 30 and 20 kya [7,16,17]. Considerable caution must be exercised in comparing dates of haplogroup coalescence, as different investigators use different mutation rates, calibration methods and coalescent models [18]. It has recently become clear that some methods are more robust and less subject to

Table 1. Diagnostic markers of Native American mtDNA lineages.

				RFLP Motif	HVSI SNPs	HVSII SNPs	Coding region SNPs
A				+HaeIII 663	16290, 16319	235, 663	1736, 4248, 4824, 8794
	A2				16111, 16362	146, 153	8027, 12007
		A2a			16192		3330
		A2b			16265		11365
B				Reg. V -9 bp	16189		8281-8289 d
	B4				16217		
		B4b				499, 827	4820, 13590 , 15535
			B2				3547, 4977, 6473, 9950, 11177
X				− *Dde*I 1715 + 16517 *Hae*III	16189, 16278	153	6221, 6371, 13966, 14470
	X2					195	1719
		X2a			16213	200	8913, 12397, 14502
C				-Hinc II 13259, +Alu I 13262, +Alu I 10287, +DdeI 10284	16327	249d	3552A, 9545, 11914, 13263, 14318
	C1				16325	290-291 d	
		C1b				493	
		C1c					1888, 15930
		C1d			16051		7697
	C4						2232A, 6026, 11969, 15204
		C4c			16245		11440, 13368, 14433, 15148
D				Alu I 5176, +Alu I 10287, +Dde I 10284	16362		4883, 5178A
	D4						3010, 8414, 14668
		D4h3			16301, 16342	152	3396, 3644, 5048
		D1*			16325		2092
		D2*			16129, 16271		3316, 7493, 8703, 9536, 11215
			D2a				11959
				D2a1a			9667, 8910A
				D2a1b	16111, 16366		9667
		D4b1*			16319		8020, 10181, 15440, 15951

* Intermediate lineages linking D4 with D1, D2, and D4b1 not shown.

Lineages are defined by either the presence or absence of specific restriction sites or deletions (RFLP Motif), or by the joint occurrence of single nucleotide polymorphisms in either of the hypervariable regions or coding region of the mtDNA molecule. SNP numbers refer to nucleotide position in the revised Cambridge Reference Sequence [48].

Table 2. Diagnostic SNP markers present in common Native American Y-chromosome lineages (bold).

	Defining mutations
C[1]	$RPS4Y_{711}$, M216, P184, P255, P260
C3	M217, PK2, P44
C3b	P39
Q[1]	M242
Q1	P36.2
Q1a	MEH2
Q1a3	M346
Q1a3a	M3
Q1a3a1	M19
Q1a3a2	M194
Q1a3a3	M199, P106, P292

[1]Y-chromosome haplogroups C and Q are the only unequivocal founding Y-haplogroups. Other Y-haplotypes are observed in Native American populations, which may represent either additional founding lineages or the result of historic admixture. After [23].

systematic error than others [19,20], but not all estimation and calibration methods have been thoroughly evaluated.

Y-chromosome variation

The paternally inherited, non-recombining portion of the Y-chromosome (NRY) is a complement to maternally inherited mtDNA. Unfortunately, high historical rates of male-mediated admixture into Native American communities have complicated the identification of Native American-specific Y chromosomes. One estimate places the degree of paternal admixture at 0.166 ± 0.02 [21], indicating that over 16% of the more than 450 Y-chromosomes examined in Greenlandic Inuit samples derive from non-native populations. Analyses of NRY single nucleotide polymorphisms (SNPs) and short tandem repeats (STRs) have identified two major Native American Y-chromosomal haplogroups, Q and C [22–24].

As with mtDNA, the identification of founding lineages within the major haplogroups is necessary for an accurate reconstruction of population history. The two most common founding NRY lineages within Native American populations are Q-M3 (also called Q1a3a), and C-3b (Table 2) [22–24]. Like mtDNA, analysis of Native American Y-chromosome lineages show reduced genetic variability, and the current distribution of Y haplotypes seems to reflect the effects of genetic drift [22]. Estimates of the age of the Q-M3 haplotype have varied considerably from study to study, (range: 7–30 kya) using STR and/or SNP data [25–28]. In contrast, Zegura *et al.* [24] found an average coalescent age for both Q and C haplogroups, using combined STR and SNP data sets, to be 17,200–10,100 YBP regardless of the estimation method used.

Autosomal DNA

Only one major study [29] has extensively surveyed Native American autosomal markers in a large sample from 24 populations throughout the Americas. Consistent with mtDNA and yDNA findings, these authors found Native American autosomal genomic diversity to be around 6.5% lower than pooled, global heterozygosity estimates. They also found evidence of substantial geographic structure in autosomal marker frequencies as measured by the correlation of the decline in genetic variation with distance from the Bering Strait. Recently, Schroeder *et al.* [30] examined the haplotype backgrounds of the private Native American allele of D9S1120 and determined that all are identical by descent. Given the rarity of this allele in potential Asian source populations, these authors conclude that the Americas were originally colonized from a single founding population. Although the signal of geographic structure and lineal ancestry is typically not as obvious in nuclear markers due to reduced geographic differentiation and haplotype sharing [11], the accumulation of extensive nuclear marker data to complement the uniparentally inherited systems is critical to provide the genetic resolution required to test alternative hypotheses of American colonization.

Alternative Migration Scenarios

Although the traditional model of New World colonization posits a single, rapid migration (containing all founding haplotypes) across the Beringian land bridge, alternative peopling scenarios have been proposed. For instance, Schurr and Sherry [31] proposed a Pacific coastal migration (containing only lineages from haplogroups A, B, C, and D) from Siberia to South America around 20–15 kya , followed by a second migration (containing haplogroup X) into North America once the ice-free corridor appeared. This model is congruent with Perego *et al.*'s [13] recent dual migration model based on the geographic distribution of two rare mtDNA lineages. D4h3 is distributed only along Pacific coastal regions of North and South America, while X2a is restricted to northeastern North America. Perego *et al.* [13] interpreted this distribution to indicate one coastal migration route and a separate, but contemporaneous, migration into the interior of North America through the ice-free corridor. The distribution of these lineages confirms strong geographic structure of mitochondrial and autosomal diversity in the Americas. Geographic structure in mtDNA haplogroup frequencies appears to be of some considerable antiquity (more than 2,000 years) based on limited aDNA data [32].

Substantial geographic structure, and at least one coastal entry is also implied by the distribution of mtDNA haplogroup B. This haplogroup has not been observed in northern populations of North America and is also rare in the southern cone of South America. In the absence of evidence for selection against this haplogroup at high latitudes, the distribution of haplogroup B may reflect a more southerly, coastal introduction and the subsequent result of drift as small populations continued a southward dispersal.

In contrast, Fagundes *et al.* [11] conclude that Native American ancestors colonized northeast Asia, including Beringia, prior to the Last Glacial Maximum (LGM). During the LGM, this population experienced a significant reduction — perhaps to as few as 1000 women — but expanded again

between 19 and 15 kya, resulting in the colonization of the Americas via a coastal route. This colonization scenario is consistent with the archaeological record in Siberia, which indicates a near abandonment of northeast Siberia at the onset of the last glacial cycle, and its recolonization by population expansion following the LGM [6,15]. In a reanalysis of data of Kitchen *et al.* [10], Mulligan *et al.* [33] conclude that ancestral Americans dispersed southward around 16 kya after divergence from the central Asian gene pool and a 7,000–15,000 year pause, presumably within Beringia, during which genetic variation accumulated.

Both single and dual migration scenarios have been alternately favored in analyses of the distribution and coalescence dates of Y-chromosome lineages in the Americas and Siberia [22,25]. A current model from Y-chromosome data posits a polymorphic population in the Altai Mountain region of Siberia as the starting point for a single, post-LGM migration between 17.2 and 10.1 kya [24]. A single-origin model from the same region was earlier proposed from mtDNA data [34,35]. It is useful to recall, however, that a single origin does not necessarily mean a single migration.

Patterned Diversity and Founder Effects

The reduced level of genetic diversity among Native Americans, with both classical and molecular markers, is consistent with the expectation of small founding populations. Mitochondrial diversity is reduced relative to the number of haplogroups found in the Americas, as is also true for Y-chromosome haplotypes.

A number of investigators have examined aspects of American colonization via simulations [36–38] based on demographic parameters derived from ethnographic research on hunter-gatherers and the spatio-temporal distribution of early archaeological sites in the Americas. Although they disagree in the particulars, these simulations demonstrate that it is possible that a small founding population could be sufficiently fertile and mobile to account for the distribution and size of Native American populations at the time of European contact. However, it may be argued that this is unlikely given the high prior probability of extinction of any very small founding population [36]. In addition, such a model does not easily account for the observed geographic structure in most genetic data.

Fix [39] used forward simulation of colonizing populations in conjunction with observed mtDNA diversity among Native American populations and concluded that no realistic demographic scenario of a single, small colonizing population dispersing southward between the continental ice sheets could result in the observed geographic distribution of genetic variation between groups (measured by the fixation index, F_{ST}). However, a separate simulation demonstrated that the distribution of F_{ST} values among Native American populations could be obtained if the colonization took place via coasts rather than the interior of the continent [40]. This result anticipated recent molecular results [11,13,29].

Beringian Scenarios

Recently, analyses and simulations have documented more extensive molecular diversity in the Americas [10,11,33,41]. All arrive at very similar time estimates for the coalescent of the Native American mtDNA haplogroups, just prior to or immediately after the LGM. These analyses are sophisticated advances on prior work and are clearly motivated by and consistent with genetic data, with several hypothesizing

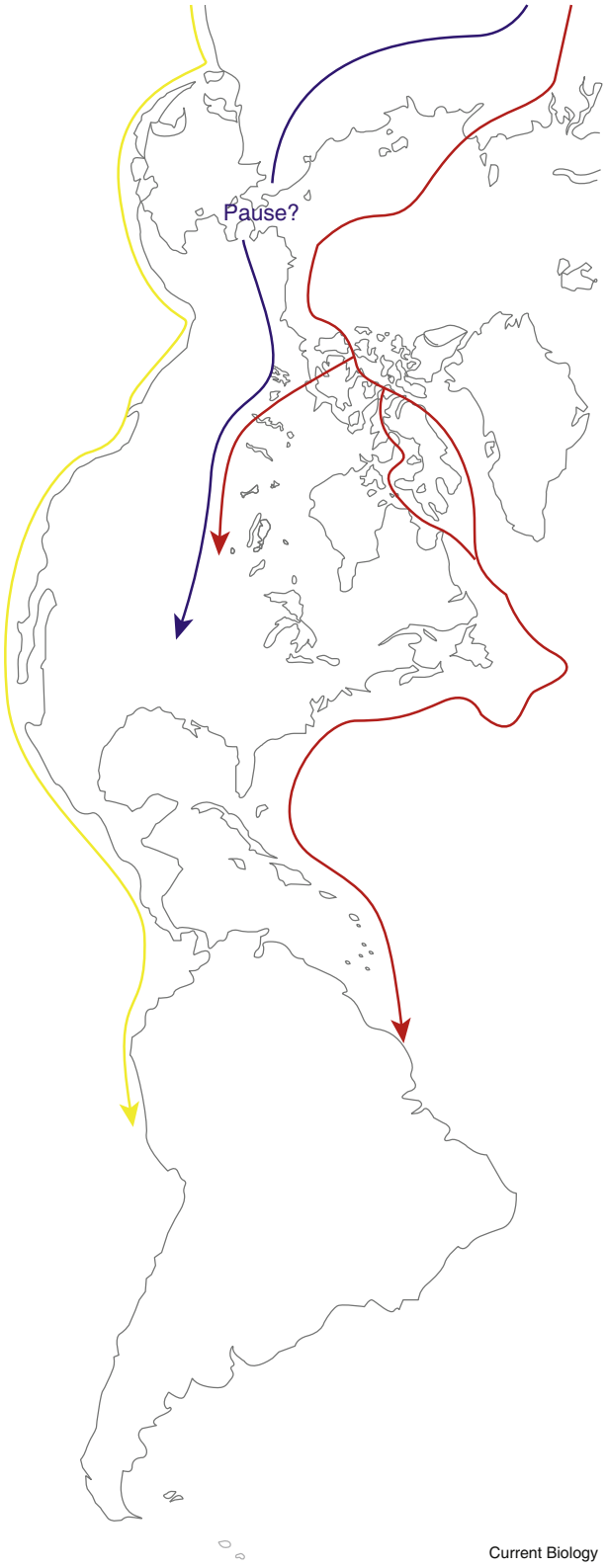

Figure 1. Hypothesized routes for original migration into the Americas. The Beringian and Pacific coastal routes (blue and yellow, respectively) may have been roughly contemporaneous following the Last Glacial Maximum (LGM), although contemporaneity is not certain. The more hypothetical northern migration path (red) implies a pre-LGM population movement. These migration paths need not be considered mutually exclusive.

a large, stable population in Beringia prior to a late American entry and dispersal. Several issues remain to be addressed in such a model of American colonization: first, despite the fact that much of interior Beringia remains in contemporary Alaska and northeast Siberia, no archaeological evidence of this population in residence has been found; second, a resident, presumably stable and possibly growing, population in Beringia seems an unlikely candidate for reduced genetic variability as a result of founder effect; third, the restricted genetic variation observed among Native Alaskan populations (only haplogroups A and D are present throughout northern North America) seems inconsistent as a source area for the more extensive genetic variation observed in the rest of the Americas. Nevertheless, these analyses raise a number of questions to be pursued by future investigators, and have initiated a challenge to long accepted views on American colonization.

This latter contribution is particularly important. As neither archaeological nor genetic data have yet been able to unequivocally resolve many of the longstanding questions regarding American colonization, the generation of new models and hypotheses to which new and more powerful analyses may be applied is essential. In this spirit, we illustrate an alternative migration route from north Asia to the Americas (Figure 1). As a coastal migration scenario to the Americas has gained currency, it is useful to recall that Beringia had two coastlines, northern and southern. People were inhabiting the north coast of Beringia very early (>30 kya). If they were exploiting coastal resources, foraging movement along that coast in the early stages of the last glacial cycle could easily have resulted in occupation of the north coast of modern Alaska prior to the LGM [42]. Accordingly, movement to the interior of the continent via the McKenzie river drainage prior to the LGM is plausible. Moreover, if, as some simulations suggest, the Innutian ice sheet formed late in the last glacial cycle, open coastal areas for continued movement eastward would have provided access to the open water of Baffin Bay and Davis Straight, and a coastal route south along the eastern seaboard of North America. If humans were indeed present in eastern North America early, before the-LGM, these populations would have been able to exploit ecologically rich intertidal zones as sea level continued to drop through the LGM. Once south of the developing ice masses, movement to coastal South America might be expected to proceed more rapidly than migration of groups located in the interior of the continents.

This scenario is, of course, speculative. It does have the advantage of bringing Asian populations to eastern North America early, to serve as a source for the development of Clovis, in the region where Clovis artifacts are found early and in highest density. It also provides a geographically shorter route to both the interior and the east coast of North America than alternative scenarios, and requires movement of populations from an interior Siberian source population in regions that share the most mt- and yDNA haplotypes with modern Native American populations. The implied early migration to the western hemisphere also is consistent with some genetic coalescent estimates predating the LGM; although it is important to recognize that such estimates contain little geographic information. Irrespective of the *a priori* likelihood of such a colonization scenario, it emphasizes, as do many of the other recent studies, the necessity of considering alternative migration hypotheses that can be subjected to rigorous tests using high resolution genetic and paleoenvironmental data in conjunction with the archaeological record.

Conclusions and Outlook

Complete agreement between mtDNA, Y-chromosomal DNA and autosomal genetic systems has not yet been realized with respect to colonization models, although all three are consistent in failing to support the 'blitzkrieg' or 'three-wave' migration models. Nevertheless, these models and their underlying assumptions continue to be used as the framework for hypothesis testing in American colonization scenarios. Dillehay [43] recently suggested that the nature of different data sets relating to continental origins — e.g., archaeology, genetics, and paleoecology — are sufficiently diverse that it is not realistic to expect concordance across them with respect to origin models. At the analytical level this is certainly true. We suggest, however, that there is one area where some degree of concordance should be helpful and measurable. It has become clear that appropriate calibration of coalescent estimates of lineage divergence is critical to our understanding of colonization events [19] and that some methods are more robust and yield more reliable dates than others [20]. Given the well-known time-dependency of mutation rates for calibrating molecular evolution, using reliable internal calibration points is essential. The use of well-dated ancient DNA samples from archaeological contexts provides perhaps the best opportunity to refine calibrations of lineage divergence in the temporal window relevant for the peopling of the Americas [44,45].

There is an unquestionable need for more genetic data from under-sampled geographic regions, as well as from more, and more widely dispersed, ancient populations. Because of the presumed nature of the colonization, reconstructing the genetic history of the Americas should be relatively simple compared to the challenges presented by other continents, but genetic analyses of American populations continue to be hindered by inadequate geographic (and temporal) sampling, lack of standardization of analytical methods, and the heterogeneous patchwork of diversity resulting from post-contact admixture. As modern archaeological research has increasingly brought into question traditional interpretations of American colonization, we view it as a necessity that archaeological and genetic research into the colonization of the Americas proceed in tandem; with the results of each enterprise informing the future hypotheses and tests of the other.

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