

MINI-REVIEW

mtDNA diversity analysis in Amerindians and other human populations - how different are they?

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THE PROBLEM

A significant part of the history of American natives has been written from information obtained with genetic studies at the protein (Salzano and Callegari-Jacques, 1988; Cavalli-Sforza *et al.*, 1994), nuclear DNA (nDNA; Guerreiro *et al.*, 1992; Deka *et al.*, 1994; Franco *et al.*, 1994; Guedez *et al.*, 1994; Petzl-Erler and McDevitt, 1994; Yunis *et al.*, 1994; Bevilacqua *et al.*, 1995; Heidrich *et al.*, 1995; Pena *et al.*, 1995; Santos *et al.*, 1995; Garber *et al.*, 1996; Parr *et al.*, 1996; Kunst *et al.*, 1996; Santos *et al.*, 1996), and mitochondrial DNA (mtDNA; Ward *et al.*, 1991; Torroni *et al.*, 1992, 1993a, 1994a; Horai *et al.*, 1993; Shields *et al.*, 1993; Merriwether *et al.*, 1994, 1995; Bailliet *et al.*, 1994; Rothhammer and Bianchi, 1995; Torroni and Wallace, 1995) levels. These works have revealed that the peopling of the Americas took place with the passing of Asiatic nomadic hunters from Northeast Asia to Alaska, during the last glaciation, through one or more migratory waves (other hypotheses have suggested other routes, for instance from Polynesia and/or Africa to America, but they are not supported by hard evidence; Cavalli-Sforza *et al.*, 1994; Bonatto *et al.*, 1996). These studies have also indicated that the American natives show low genetic variability when they are compared with other human

groups. Some investigators supported the idea that the colonization from Asia into the American continent, as well as from Central America to South America through the Isthmus of Panama, was accompanied by severe bottlenecks that markedly restricted the levels of genetic diversity in American natives (Wallace *et al.*, 1985; Chakraborty and Weiss, 1991; Wallace and Torroni, 1992; Batista *et al.*, 1995), although others hold an opposite view (Bailliet *et al.*, 1994; Monsalve *et al.*, 1994; Bianchi *et al.*, 1995). This particularity and others, like population structure, habitat diversity and specific cultural processes may have been responsible for several of the genetic characteristics presently observed among Amerindians. It is not clear, however, what is the relative importance of these factors in the explanation of Amerindian evolution. Few studies also considered the partition of the total genetic variation into intra vs. interpopulational diversity. The present review was undertaken to answer the following questions: a) how is DNA data contributing to clarify the question whether Amerindians are less variable than people from other ethnic groups? b) are there significant differences in genetic diversity among North, Central and South American Indians? c) do different approaches lead to different responses to these questions? and d) what results are obtained when the total variability is partitioned into intra and interpopulational levels? Since much more information is available at the mtDNA than at the nDNA levels, we concentrated our attention on the former, and for the

same reason examined data from restriction enzyme studies rather than sequence results.

THE DATA AND ITS ANALYSIS

Population frequencies of mtDNA haplotypes and haplogroups were estimated from data of earlier studies (Schurr *et al.*, 1990; Torroni *et al.*, 1993a,b, 1994a,b; Ward *et al.*, 1993, 1996; Merriwether *et al.*, 1994, 1995; Chen *et al.*, 1995). To characterize the variability of each haplogroup we calculated the frequencies of variant sites defined by specific restriction enzymes, using data from Torroni *et al.*, 1993a,b, 1994a,b; Chen *et al.*, 1995. Nei's measures of gene diversity (Nei, 1986, 1987) were used to quantify the degree of total (H_t), intra (H_s) and inter-population (D_{ST}/D_m) genetic variability, and to estimate the percentage of genetic variation attributable to interpopulational diversity (or gene differentiation coefficient, $G_{ST}/G_{ST'}$). All analyses were performed using the DISPAN computer program (Ota, 1993).

RESULTS AND DISCUSSION

Table I shows the values of genetic diversity for 41 American natives, considering just the haplogroup frequencies. The total diversity (H_t) ranges from 0.39 (Na-Dene) to 0.74 (South Amerindians), while the average intra-population variability (H_s) varies from 0.34 (Na-Dene) to 0.63 (North Amerindians). The Haida and Dogrib present mainly haplogroup A, and should be responsible for the low H_t values among the Na-Dene (Torroni *et al.*, 1993a; Bailliet *et al.*, 1994; Merriwether *et al.*, 1995), while the A, B, C and D haplogroups are represented in the majority of the North and South Amerindian tribes (Ward *et al.*, 1991; Torroni *et al.*, 1992; Horai *et al.*, 1993; Kolman *et al.*, 1995). Most of the Central American tribes, on the other hand, exhibit only A and B haplogroups, justifying the intermediate H_t value (Batista *et al.*, 1995;

Table I - Gene diversity analysis of 41 American native populations using the frequencies of five categories of mtDNA haplogroups (A, B, C, D and others)¹.

Population	N	Haplogroup diversity			
		Total diversity (H_t)	Within population (H_s)	Between populations (D_m)	Percentage interpopulation diversity
<i>Na-Dene</i>	290	0.39	0.34	0.07	17
Haida	63	-	0.12	-	-
Apache	25	-	0.55	-	-
Dogrib	154	-	0.17	-	-
Navajo	48	-	0.52	-	-
<i>North Amerindians</i>	284	0.74	0.63	0.13	18
Chipewa	15	-	0.75	-	-
Mohawak	18	-	0.69	-	-
Oneota	50	-	0.62	-	-
Muskoke	71	-	0.69	-	-
Bella-Coola	57	-	0.52	-	-
Nuu-Chah-Nulth	15	-	0.75	-	-
Pima	30	-	0.57	-	-
Ojibwa	28	-	0.53	-	-
<i>Central Amerindians</i>	137	0.51	0.41	0.11	22
Maya	27	-	0.67	-	-
Teribe	20	-	0.33	-	-
Guatuso	20	-	0.26	-	-
Boruca	14	-	0.46	-	-
Kuna	16	-	0.00	-	-
Huetar	27	-	0.45	-	-
Guaymi	16	-	0.44	-	-
Mixtec	29	-	0.52	-	-
Mixe	16	-	0.30	-	-
Zapotec	15	-	0.69	-	-
Cabecar	24	-	0.51	-	-
<i>South Amerindians</i>	598	0.74	0.58	0.16	22
Mataco	28	-	0.58	-	-
Aymara	172	-	0.51	-	-
Quechua	19	-	0.71	-	-
Mapuche	39	-	0.73	-	-
Pehuenche	100	-	0.59	-	-
Huilliche	80	-	0.65	-	-
Atacameno	50	-	0.46	-	-
Ticuna	28	-	0.63	-	-
Yanomama	24	-	0.61	-	-
Makiritare	10	-	0.48	-	-
Macushi	10	-	0.74	-	-
Wapishana	12	-	0.51	-	-
Kraho	14	-	0.59	-	-
Marubo	10	-	0.57	-	-
Xavante	25	-	0.27	-	-
Zoró	29	-	0.56	-	-
Gavião	5	-	0.35	-	-
Piaroa	10	-	0.61	-	-
<i>Native Americans</i>	1123	0.73	0.51	0.23	31

¹Data were compiled from Schurr *et al.* (1990), Ginther *et al.* (1993), Torroni *et al.* (1993a, 1994a), Ward *et al.* (1993, 1996), Merriwether *et al.* (1994, 1995). Estimates were calculated according to Nei (1986, 1987).

Merriwether *et al.*, 1995). The percentages of genetic variation attributable to interpopulational diversity vary from 17% (Na-Dene) to 22% (Central and South Amerindians).

Table II presents information about the mtDNA diversity in Amerindian tribes considering a more restricted set of populations, but using the information obtained from the distribution of 96 haplotypes defined by 14 restriction enzymes. *Ht* ranges from 0.76 (Na-Dene) to 0.95 (South American tribes), and the average intrapopulational variability (*Hs*) from 0.52 to 0.86 in Central and North Amerindians, respectively. These values are considerably larger than those obtained considering haplogroups only, as expected since the

number of variables increased markedly. The tendency of more diversity in the Na-Dene → Central Amerindians → North/South Amerindians direction can also be observed here. The lowest proportion of genetic variation attributable to interpopulational diversity was obtained among the North Amerindians (8%), and the largest among the Central Amerindians (47%). The low North Amerindian frequency cannot be easily explained, since the Pima and Ojibwa are located geographically far apart, show different levels of admixture with Caucasian populations (1% and 30%, respectively; Szathmary *et al.*, 1974; Szathmary, 1983; Williams *et al.*, 1985), and belong to distinct linguistic subaffiliations (Greenberg, 1987; Torroni *et al.*, 1992; Cavalli-Sforza *et al.*, 1994). It is possible that specific haplotypes of the Pima and Ojibwa may have been lost, creating an artificial genetic similarity. On the other hand, the Na-Dene value (12%), is expected since the Dogrib and Navajo are genetically (Szathmary, 1983) and linguistically (Greenberg, 1987) closely related. The high Central American value is surprising, since of the six tribes considered, five are Chibcha-speakers. But earlier studies have also observed the existence of a high level of genetic microdifferentiation among the Chibcha tribes, which may have resulted from a particular type of geographical dispersion, which differs from the traditional fission-fusion model (Barrantes *et al.*, 1990; Barrantes, 1993).

The Amerindian results are compared with those obtained for Siberians, Caucasians and Africans in Table III. Two sets of comparisons are shown, one considering just haplogroup categories, and the other the haplotypes defined by the 14 restriction enzymes listed in Table II. Total diversity is not much different in the four population groups, but there is a striking diversity in its fraction of total variability due to the interpopulational diversity, Amerindians and Siberians showing 5x more heterogeneity than Caucasians (31%; 30%; 6%, respectively) when haplogroup heterogeneity is considered. The differences between Amerindians on one hand, and Siberians or Africans on the other, are also large (respectively, 30%, 18% and 12%) when the comparison is made with haplotypes. The fact that Amerindians and Siberians are not much different when

Table II - Gene diversity analysis of 20 American native populations considering mtDNA haplotypes¹.

Population	N	Haplotype diversity ²			
		Total diversity (<i>Ht</i>)	Within population (<i>Hs</i>)	Between populations (<i>D_{ST}/D_m</i>)	Percentage interpopulation diversity
<i>Na-Dene</i>	58	0.76	0.67	0.09	12
Dogrib	30	-	0.54	-	-
Navajo	28	-	0.82	-	-
<i>North Amerindians</i>	58	0.93	0.86	0.07	8
Pima	30	-	0.92	-	-
Ojibwa	28	-	0.83	-	-
<i>Central Amerindians</i>	137	0.86	0.52	0.40	47
Maya	27	-	0.91	-	-
Teribe	20	-	0.33	-	-
Guatuso	20	-	0.35	-	-
Boruca	14	-	0.47	-	-
Kuna	16	-	0.12	-	-
Guaymi	16	-	0.79	-	-
Cabecar	24	-	0.75	-	-
<i>South Amerindians</i>	120	0.95	0.71	0.22	26
Ticuna	28	-	0.92	-	-
Yanomama	24	-	0.83	-	-
Makiritare	10	-	0.72	-	-
Macushi	10	-	0.93	-	-
Wapishana	12	-	0.61	-	-
Kraho	14	-	0.83	-	-
Marubo	10	-	0.76	-	-
Piaroa	10	-	0.82	-	-
<i>Native Americas</i>	373	0.94	0.67	0.29	30

¹ Haplotypes were defined by 14 restriction enzymes: *AvaI*, *AvaII*, *DdeI*, *HaeIII*, *HhaI*, *HinfI*, *HpaI*, *HpaII*, *MboI*, *RsaI*, *TaqI*, *BamHI*, *HaeII*, *HincII*, and by the presence of the 9 bp-deletion occurring between the COII and tRNA^{Lys} genes (Torroni *et al.*, 1992, 1993a).

² The interpopulational diversity (*D_{ST}*) and the percentage of total variability attributable to interpopulation diversity (*G_{ST}*) are known to be affected by the number of subpopulations examined; therefore *D_m* and *G_{ST}* (Nei, 1986) have been used when the number of subpopulations is larger than two.

For the sources of the data and references to the methods used see Table I footnotes.

haplogroups are considered, but show differences at the haplotype level, may indicate a higher rate of genetic differentiation in America, compared with that which has occurred in Siberia. The Amerindian percentage of interpopulation diversity is larger than that observed in previous studies, which considered, however, data from classical genetic polymorphisms (Livshits and Nei, 1990; Cavalli-Sforza *et al.*, 1994; Bortolini *et al.*, 1995, in press), nuclear DNA (Deka *et al.*, 1995; Bevilaqua *et al.*, 1995; Zago *et al.*, 1996), and mtDNA D-loop sequence results (Bortolini, M.C., Zago, M.A., Salzano, F.M., Silva-Jr., W.A. and da Silva, M.C.B.O., unpublished results).

The distributions of specific variant sites in the A, B, C and D haplogroups are presented in Table IV. As can be verified, the degree of variation for each specific site is generally low (below 15%), except for site 16517e. This information was used to organize Table V, in which these results are compared with those obtained for Caucasoid- and African-derived haplogroups. A and C are about equally variable, D comes afterwards, and B is the least variable (3x less) as was already observed in earlier studies (Torrioni *et al.*, 1993a). The variability within Caucasian characteristic haplogroups ranges from 0.01 (K) to 0.04 (H), while the values for L₁ and L₂ are 0.08 and 0.56, respectively. The African haplogroups show the highest total diversity (0.09) and the Amerindian haplogroups the lowest (0.04). These results confirm tendencies already observed in previous investigations that used, however, the proportion of sequence divergence to estimate the variability (Torrioni

et al., 1993a,b; Chen *et al.*, 1995). Interestingly, the percentage of interhaplogroup diversity obtained in Amerindians (59%) is intermediate between those observed in Caucasians (73%) and Africans (27%). This last value is equal to that calculated from the proportion of sequence divergence obtained by Chen *et al.* (1995).

CONCLUSIONS

We can now try to answer the questions posed in the introduction. Although American Indians are less variable in total diversity considering classical and nuclear DNA markers, this is not true for mtDNA polymorphisms. Their total diversity, either comparing characteristic haplogroups or a given set of haplotypes defined by 14 restriction enzymes, is of the same order of magnitude as those obtained in other ethnic groups. Moreover, they present at the mtDNA level a degree of interpopulational variability that is higher than those found elsewhere. Here they confirm the classical polymorphism results. Cavalli-Sforza *et al.* (1994), after considering average F_{ST} values based on these markers, concluded that "America, in particular South America, is genetically the most variable part of the world" (p. 337).

The main difference among the mtDNA of Amerindians, independent of the two methods of study employed in the present review, resides in the low variability observed among the Na-Dene tribes. The

Table III - Gene diversity analysis comparing different ethnic groups¹.

Populations		No. of individuals	No. of populations	Total diversity (<i>Ht</i>)	Within population (<i>Hs</i>)	Between populations (<i>Dm</i>)	Percentage interpopulation diversity
American natives	(1)	1123	41	0.73	0.51	0.23	31
	(2)	373	20	0.94	0.67	0.29	30
Siberians	(1)	413	10	0.71	0.49	0.26	33
	(2)	153	3	0.93	0.80	0.18	18
Caucasoids	(1)	51	3	0.67	0.64	0.04	6
	(2)	-	-	-	-	-	-
Africans	(1)	127	5	0.65	0.52	0.16	24
	(2)	127	5	0.97	0.88	0.12	12

¹Sources of data for the American natives and the methods employed are indicated in Table I footnotes. (1) Analysis using haplogroup categories A, B, C, D, and others; H, I, J, K, and others, L₁ and L₂, and others as units; (2) analysis using haplotypes defined by 14 restriction enzymes listed in Table II footnotes as units. Siberian populations considered in: (1) Eskimos, Chukchi, Koryaks, Yukagirs, Evens, Nivkhs, Udegeys, Evenks, Nganasans and Sel'kups. Source: Torrioni *et al.* (1993b); in (2) Nivkhs, Evenks, and Udegeys. Source: Torrioni *et al.* (1993b); Caucasoid populations: (1) Italian, Canadian and British. Source: Torrioni *et al.* (1994b); African populations: (1) and (2) Wolof, Mandenkalu, Pular, Eastern Pygmies, Western Pygmies. Source: Chen *et al.* (1995).

Table IV - Percentages of the presence of restriction sites in A, B, C and D haplogroups of American natives.

Site ¹	Haplogroups				Site ¹	Haplogroups			
	A (156)	B (93)	C (61)	D (59)		A (156)	B (93)	C (61)	D (59)
1) 8e	0	1.1	0	0	48) 8774a	0	1.1	0	0
2) 29c	0	0	8.2	0	49) 9052n/9053f	90.4	98.9	98.4	100
3) 64c	0	0	0	1.7	50) 9253e	0	0	1.6	0
4) 104i	82.1	100	100	100	51) 9342e	97.4	100	100	100
5) 663e	100	0	0	0	52) 9504a	0	0	1.6	0
6) 717g	0	0	0	96.6	53) 9714e	0	2.1	0	0
7) 931i	98.7	100	98.4	100	54) 9942j	0	1.1	0	0
8) 1004h	0.6	0	0	0	55) 9953e	100	100	100	96.1
9) 1622n/1623f	0	0	1.6	0	56) 10097e	0.6	0	0	0
10) 2113j	0	0	0	1.7	57) 10394c	11.0	100	96.7	98.3
11) 2247c/2250a	0.6	0	0	0	58) 103/97a	100	100	96.7	98.3
12) 2636e	6.4	0	0	0	59) 10893l	0	5.4	0	0
13) 2849k	99.4	100	100	100	60) 11074c	0	0	1.6	0
14) 3192c	100	98.9	100	100	61) 11100a	0	0	1.7	0
15) 3315e	93.6	100	100	100	62) 11327a	0	1.1	0	0
16) 3337k	100	100	100	98.3	63) 11793c	0	0	1.6	0
17) 3371k	0	0	4.9	0	64) 11892a	0.6	0	0	0
18) 3388c/3391a	0	1.1	1.6	0	65) 11924l	0	0	1.6	0
19) 3397k	0	0	0	8.4	66) 11974k	0	1.1	0	0
20) 3412e	100	100	98.4	100	67) 12026h/o	0	0	0	3.4
21) 3534c	97.4	100	100	100	68) 12891c	100	100	100	98.3
22) 3846c/3849e	2.6	0	0	0	69) 13031g	100	98.9	100	100
23) 3981a	0	0	8.2	0	70) 13259o	98.7	100	100	100
24) 3987k	0	1.1	0	0	71) 13259o/13262a	100	100	1.6	100
25) 4051k	0	0	11.5	0	72) 13268g	100	100	100	88.0
26) 4310a	99.4	100	100	100	73) 13633e/13634o	0	0	1.6	0
27) 4546g	1.3	0	0	0	74) 14015a	99.4	100	100	100
28) 4848e	100	100	100	94.9	75) 14304a	100	96.8	100	100
29) 5054k	100	100	98.4	0	76) 14858n/14859f	100	100	96.8	100
30) 5164k	2.6	0	0	0	77) 15002n/15033f	100	100	93.4	100
31) 5176a	100	100	100	0	78) 15073c	98.7	100	100	96.6
32) 5351f	0	1.1	0	0	79) 15172e	99.4	97.8	100	100
33) 5584a	100	1	98.4	0	80) 15245a	0	0	1.6	0
34) 5983g	100	97.8	100	100	81) 15127c	0	0	1.3	0
35) 6204a	100	100	100	94.9	82) 15776a	97.4	100	99.4	100
36) 6618e	2.6	0	0	0	83) 16049k	100	100	90.4	100
37) 7013k	100	100	85.3	100	84) 16145e	0	0	1.6	0
38) 7497e	98.7	96.8	100	100	85) 16145j	0	2.1	0	3.4
39) 7607e	3.2	0	0	0	86) 16224l	0.6	1.0	0	0
40) 7750c	100	100	98.4	100	87) 162381l	0.6	0	0	0
41) 7853o	100	98.9	100	100	88) 16240a	0	3.2	0	0
42) 7959j	100	100	98.4	100	89) 16329k	86.5	100	100	100
43) 7897k	93.6	100	100	100	90) 16389g/16390b	1.3	0	0	0
44) 7979e	0	1.1	0	0	91) 16389m/16390j,b	0.6	0	0	0
45) 8269k	0.6	0	0	0	92) 16456e	99.4	100	100	100
46) 8565j	0	0	11.5	0	93) 16494i	0	0	0	6.8
47) 1569c/8572e	1.9	0	0	0	94) 16517e	18.6	100	32.8	28.8
					95) 9-bp.delet.	0.6	100	0	0

¹Sites are numbered from the first nucleotide of the recognition sequence, according to the reference sequence (Anderson *et al.*, 1981). The restriction enzymes used in the analysis are designated by the following single-letter code: a = *AluI*; b = *AvaII*; c = *DdeI*; e = *HaeIII*; f = *HhaI*; g = *HinfI*; h = *HpaI*; i = *HpaII*; j = *MboI*; k = *RsaI*; l = *TaqI*; m = *BamHI*; n = *HaeII*; o = *HincII*.

Table V - Diversity analysis in the A, B, C, D, H, I, J, K, L₁ and L₂ haplogroups¹.

Haplogroup (N)	Parameters of diversity ²			Percentage interhaplogroup diversity
	Ht	Hs	D _{ST/Dm}	
A + B + C + D (369)	0.04	0.02	0.02	59
A (156)	-	0.02	-	-
B (93)	-	0.01	-	-
C (61)	-	0.02	-	-
D (59)	-	0.02	-	-
H + I + J + K (109)	0.07	0.02	0.06	73
H (68)	-	0.04	-	-
I (13)	-	0.02	-	-
J (16)	-	0.03	-	-
K (12)	-	0.01	-	-
L ₁ + L ₂ (107)	0.09	0.07	0.03	27
L ₁ (48)	-	0.08	-	-
L ₂ (59)	-	0.06	-	-
A + B + C + D + H + I + J + K + L ₁ + L ₂ (585)	0.28	0.07	0.23	78

¹A, B, C and D haplogroups were defined by Asian/Asian-derived specific mutations; H, I, J and K by Caucasoid specific mutations (Torrioni *et al.*, 1993a, 1994b); L₁ and L₂ were defined by African specific mutations (Chen *et al.*, 1995).

²Estimates obtained according to Nei's method (1986, 1987) using the frequencies of the sites defined by 14 restriction enzymes observed in each haplogroup (Table IV).

other somewhat surprising finding was the high gene differentiation coefficient observed among the Central American Indians.

The concentration of analyses at the haplogroup level may simplify the studies, but at the same time can hide important heterogeneity. Thus, the total diversity found in A, B, C, and D haplogroups is about one-third of that observed for L₁ and L₂ haplogroups, and the share of this variability that is due to the interhaplogroup diversity is much more important (2x higher) in Amerindians than in Africans.

Many factors determine the level of diversity found in a population at a certain time. To correctly evaluate this level many approaches are necessary, at different points of the biological hierarchy. As protein, nDNA and mtDNA data accumulate we may be able to clarify at least the main outlines of our evolutionary history.

ACKNOWLEDGMENTS

Our research was supported by Financiadora de Estudos e Projetos (FINEP), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and Fundação de

Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS).

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