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Original Research Article

A Revertant of the Major Founder Native American Haplogroup C Common in Populations From Northern South America

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ABSTRACT We examined the mtDNA RFLP diversity of 17 Native American populations from Colombia. Five of the populations studied were found to have variable frequencies of a mtDNA type lacking the characteristic changes of haplogroups A-D. Sequencing of mtDNA HVS-I and II showed that this "null" RFLP type carries all the substitutions characteristic of Native American founder lineage C. A back mutation has therefore recreated the +13,259 *Hin*cII/−13,262 *Alu*I restriction sites that tipify RFLP haplogroup C. This revertant C lineage is further characterized by three changes in HVS-II sequence: C/T transitions at positions 115 and 152, and the deletion of an A residue at position 116. This lineage is observed at high frequency mostly in populations from Greenberg's Equatorial–Tucano linguistic family. Genetic structure analyses are consistent with the reversion mutation occurring at an early stage during the tribalization process. Am. J. Hum. Biol. 18:59–65, 2006.

Mitochondrial DNA (mtDNA) analyses are being used extensively to examine the diversification of human populations, including the timing and pattern of initial peopling of the American continent, and the relationship of genetic data to archaeological and linguistic information (Cavalli-Sforza and Feldman, 2003; Cavalli-Sforza et al., 1994; Crawford, 1998). Several continent-wide surveys of Native American mtDNA variation, both at the restriction enzyme and DNA sequence levels have shown that the great majority of mtDNAs in the Americas can be assigned to one of four major lineages (A–D) (Ginther et al., 1993; Horai et al., 1993; Torroni et al., 1992, 1993a). At the restriction level, lineage A is characterized by a *Hae*III site gain at position 663; lineage B by a 9-bp COII/tRNA^{Lys} intergenic deletion; lineage C by a *Hin*cII site loss and a *Alu*I site gain at positions 13,259 and 13,262, respectively, and lineage D by an *Alu*I site loss at position 5,176. At the sequence level, lineages A–D have been defined by specific nucleotide changes in the hypervariable segments of the mtDNA D-loop (Bandelt et al., 2003; Forster et al., 1996; Horai et al., 1993; Torroni et al., 1993a). These four lineages are also present in Asian populations, consistent with their introduction in the Americas by the first migrants from Asia (Ballinger et al., 1992; Kolman et al., 1996; Torroni et al., 1993b, 1994).

To date, surveys of Native American mtDNA diversity using RFLPs have examined a considerably larger number of individuals and populations than those based on DNA sequencing. Interestingly, RFLP surveys have not infrequently reported

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mtDNA haplotypes lacking the changes characteristic of haplogroups A–D, particularly in South America (Bailliet et al., 1994; Easton et al., 1996; Keyeux et al., 2002; Merriwether and Ferrell, 1996; Merriwether et al., 2000; Torroni et al., 1993a). Other than resulting from experimental problems (contamination and/or mistyping), these "null" haplotypes (sometimes denoted E, N, or X) could represent unrecognized founder lineages, recent non-Amerindian admixture or reversion mutations affecting the RFLP changes characteristic of lineages A–D. Unfortunately, these various explanations have not been systematically tested, usually because most RFLP surveys lack mtDNA sequence information.

Here we examined the mtDNA diversity of 17 Native Colombian populations by typing the RFLP changes characteristic of haplogroups A–D. Several populations from Eastern Colombia showed mtDNA type lacking the mutations characteristic of haplogroups A–D. Sequencing of mtDNA hypervariable segments I and II identified this "null" haplogroup as a revertant of founder lineage C.

SUBJECTS AND METHODS

Populations studied

The linguistic affiliation and approximate geographic location of the 17 populations studied are shown in Table 1 and Fig. 1, respectively. Additional anthropological informations about these populations can be obtained in Moreno et al. (1993). Samples of Embera, Wayuu, and Zenu were available in the laboratory of A.R.L. as anonymous DNA samples. For the other populations, samples had been collected from consenting individuals by H.G. de R. in 1987/1988, anonymized, and stored as frozen whole blood, red blood cells, white blood cells, or plasma. Genomic DNA was extracted from these last samples using Chelex 100 (Bio-Rad, Hercules, CA) according to the protocol of the supplier. This research was approved by the ethics committees of Universidad de Antioquia and Universidad de Los Andes.

RFLP analysis

Four regions of human mtDNA were amplified by PCR using the primers reported by Bailliet et al. (1994), except for primer MiH13437 which was modified based on a difference with the Andrews et al. (1999) revised Reference Sequence (5′-AG GTATGGTTTTGAGTAGTCCT-3′). Each amplification reaction was carried out using 5–10 ng of total DNA, 10 pmol of each primer, 200 μM dNTPs (Promega), 250 μg/ml BSA, 2 mM $MgCl_2$, and 1.5 U of *Taq* polymerase (Gibco-BRL) in a final volume of 25 μl. Thirty cycles of 94°C (1

TABLE 1. Frequency of the mtDNA haplogroups in the 17 Native Colombian populations examined and two proposed linguistic classifications for these populations

								Greenberg	
Population	*n*	A	B	C	D	Null	Campbell	Family	Subfamily
1 Cubeo	22	0.27	0.18	0.5	0.05	0	Tucanoan	Equatorial-Tucano	Macrotucano
2 Curripaco	5	0	0	1	0	0	Maipurean	Equatorial-Tucano	Equatorial
3 Desano	2	0.5	0	0	0.5	0	Tucanoan	Equatorial-Tucano	Macrotucano
4 Embera	22	0.76	0.24	0	0	0	Chocoan	Chibcha-Paez	Paezan
5 Guahibo	9	0.44	0	0.11	0	0.45	Guahiboan	Equatorial-Tucano	Equatorial
6 Huitoto	13	0.15	0	0.31	0.46	0.08	Huitotan	Ge-Pano-Carib	Macrocarib
7 Ingano	43	0.12	0.46	0.42	0	0	Quechuan	Andino	Quechuan
8 Jebero	1	0	0	1	0	0	Cahuapanan	Andino	Cahuapanan
9 Ocaina	2	0	0	1	0	0	Huitoan	Ge-Pano-Carib	Macrocarib
10 Paez	20	0.6	0.2	0.15	0.05	0	Paezan	Chibcha-Paez	Paezan
11 Piapoco	39	0.18	0.03	0.15	0.05	0.59	Maipurean	Equatorial-Tucano	Equatorial
12 Puinave	19	0.05	0.16	0.58	0.16	0.05	Puinavean	Equatorial-Tucano	Macrotucano
13 Saliva	13	0.15	0	0.54	0.15	0.15	Salivan	Equatorial-Tucano	Equatorial
14 Ticuna	74	0.15	0.23	0.38	0.24	0	Yuri-Ticunan	Equatorial-Tucano	Macrotucano
15 Wayuu	40	0.25	0.36	0.39	0	0	Maipurean	Equatorial-Tucano	Equatorial
16 Yagua	12	0.25	0	0.67	0.08	0	Yaguan	Ge-Pano-Carib	Macrocarib
17 Zenu*	36	0.22	0.41	0.31	0.06	0	?	?	?

Note: The Zenu currently speak Spanish, and the affiliation of the language originally spoken by this population is uncertain.

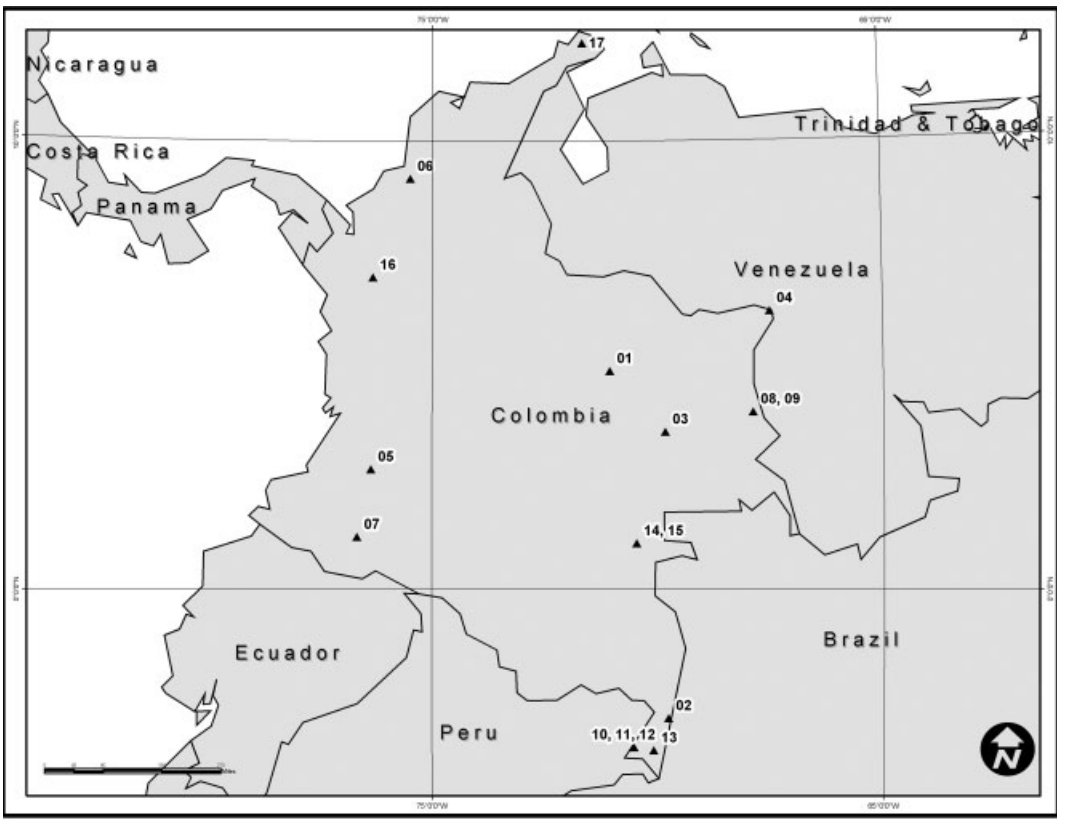

Fig. 1. Map of Colombia showing the approximate geographic location of the 17 Native American populations studied: 1, Cubeo; 2, Curripaco; 3, Desano; 4, Embera; 5, Guahibo; 6, Huitoto; 7, Ingano; 8, Jebero; 9, Ocaina; 10, Paez; 11, Piapoco; 12, Puinave; 13, Saliva; 14, Ticuna; 15, Wayuu; 16, Yagua; 17, Zenu.

min), 53°C (1 min), and 72°C (1 min) were followed by a final 5 min at 72°C. The four DNA fragments containing polymorphic sites diagnostic of haplogoups A, C, and D were digested using 13.3 μl of PCR product, 2 units of enzyme and 1.5 μl of buffer (10×) for 12 h at 37°C. Digested products were resolved in a 2.5% agarose gel, stained with ethidium bromide, and visualized by UV. The 9-bp COII-tRNA intergenic deletion polymorphisms characteristic of haplogroup B was typed by running the PCR products on a 12% polyacrylamide gel followed by ethidium bromide staining and UV visualization.

Sequencing

The hypervariable regions 1 and 2 (HV1 and HV2) of the D-loop were sequenced between nucleotides 16024–16394 (HV1) and 66–408 (HV2). Briefly, 10 ng of DNA was amplified with the primers HV1 (reported by Ward et al., 1991) and HV2 (reported by Kolman et al., 1995), respectively. The PCR product was purified by standard protocols and subjected to either fluorescent or radioactive sequencing.

Data analysis

Sequences were aligned manually. Diversity analyses were performed using the Arlequin program v. 2.0. A median-joining network analysis of the DNA sequences was carried out with the NETWORK 3.1 program (Bandelt et al., 1999).

RESULTS

The frequency of RFLP haplogroups in the populations examined are show in Table 1. Five populations from eastern Colombia show a "null" haplogroup lacking the changes characteristic of haplogroups A-D. The Piapoco and the Guahibo have particularly elevated frequencies of this null RFLP type (59% and 45%, respectively, Table 1).

We sequenced HVS-I and II in 18 out of 31 individuals with "null" RFLP haplotypes. In additional, a few individuals from each of the 17 populations studied were selected randomly for sequencing.

Among the 64 samples sequenced, 37 different HVS-I/II sequence types were observed defined by 63 polymorphic sites (Fig. 2). Four different sequence variants were identified in null RFLP haplotypes (sequences 19–22 in Fig. 2). A median-joining network analysis shows that the all the sequences obtained group into 4 major clusters (Fig. 3). Within a cluster, sequences share the nucleotide changes characteristic of lineages A–D (Fig. 2). The four sequences from null haplotypes form a discrete cluster within lineage C (Fig. 3). These sequences carry the diagnostic positions of sub-haplogroup C_1 in HVS-I (16,325) and HVS-II (290d-291d) (Bandelt et al., 2003) and share three additional changes in HVS-II: transitions at 115 and 152 plus the deletion of an A residue at position 116 (Fig. 2). Null RFLP haplotypes thus correspond to a C sublineage in which a reversion of the transition at position 13,263 has recreated the *Hinc*II 13,259 site and abolished the concomitant *Alu*I gain at 13,262 that characterize haplogroup C. Consistent with its ancestral status, the nodal revertant C sequence (number 19 in Fig. 3) is seen in all populations with null RFLP haplotypes. Furthermore, sequence 19 is derived from sequence 32, the most common C sequence observed in the Colombian popu-

Sequence type	RFLP	HVS-I (16000+)	HVS-II	Population 1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	Total
1	A	111 129 223 274 290 319 362	73 146 153 235 263				1														1
2	A	111 129 223 290 319 362	73 146 153 235 263				1														1
3	A	111 213 223 290 319 362	73 146 153 235 263									1					2				3
4	A	111 223 290 319 362	73 146 153 235 253 263																	1	1
5	A	111 223 290 319 325 362	73 146 153 235 263																	1	1
6	A	111 223 290 319 356 362	73 146 153 235 263				1					1									2
7	A	86 111 195 223 288 290 319 362	73 146 153 235 263						1												1
8	A	111 223 290 319 362	73 146 153 235 263 280																	1	1
9	A	95 111 207 223 290 319 362	73 101 146 153 235 263	1																	1
10	A	111 223 290 293 319 362	73 146 153 207 235 263																1		1
11	A	111 223 290 319 360 362	73 125 127 146 153 235 263										1								1
12	A	111 223 290 319 362	73 146 153 235 263				1												1		2
13	B	79 183C 189 217 358	73 263															1			1
14	B	183C 189 217 358	73 263															1			1
15	B	189 217 287 300 358	73 263						1												1
16	B	183C 189 217 304	73 263	1																	1
17	B	183C 189 217	73 263												1						1
18	B	182C 183C 189 217 360	73 263										1								1
19	"null"	223 298 325 327	73 115 116d 152 249d 263 290d 291d					2	1					3	1	1					8
20	"null"	223 298 325 327	73 115 116d 152 249d 263 290d 291d 372					1													1
21	"null"	223 298 325 327 362	73 115 116d 152 249d 263 290d 291d					1						6		1					8
22	"null"	93 223 298 325 327	73 115 116d 152 249d 263 290d 291d											1							1
23	C	172 223 298 325 327	73 194 207 249d 263 290d 291d	2																	2
24	C	223 298 325 327	73 194 249d 263 290d 291d								1						1				2
25	C	179A 223 298 311 325 327 356	73 249d 263 290d 291d						1												1
26	C	179A 223 298 311 325 327	73 249d 263 290d 291d													1					1
27	C	179A 223 243 298 311 325 327	73 249d 263 290d 291d												2						2
28	C	223 249 298 325 327	73 146 249d 263 290d 291d											1							1
29	C	223 297 298 325 327	73 143 249d 263 290d 291d																1		1
30	C	223 298 325 327	73 174 249d 263 290d 291d																	1	1
31	C	223 239 298 325 327	73 249d 263 290d 291d														1				1
32	C	223 298 325 327	73 249d 263 290d 291d		2					1		1						1		1	6
33	C	92 223 266 298 325 327	73 249d 263 290d 291d												1						1
34	D	189 223 325 362	73 263			1			1												2
35	D	142 223 290 325 362	73 263						1												1
36	D	127 223 300 325 362	73 196 263						1												1
37	D	223 325 362	73 263									1									1
			Total	4	2	1	4	4	7	1	1	4	2	11	6	2	4	3	3	5	64

Fig. 2. Variable nucleotide positions of the HVS-I/II mtDNA sequences obtained and their frequency in 17 Native Colombian populations. Positions are numbered after the revised Cambridge Reference Sequence (CRS) of Andrews et al. (1999). All positions are transitions, except those followed by letters "A," "C" (denoting transversions), or "d" (indicating deletions). The RFLP classification of haplotypes from which sequences were obtained is shown in the second column. Population numbers are as in Fig. 1. Variations at the 303–315 tract in HVS-II are disregarded.

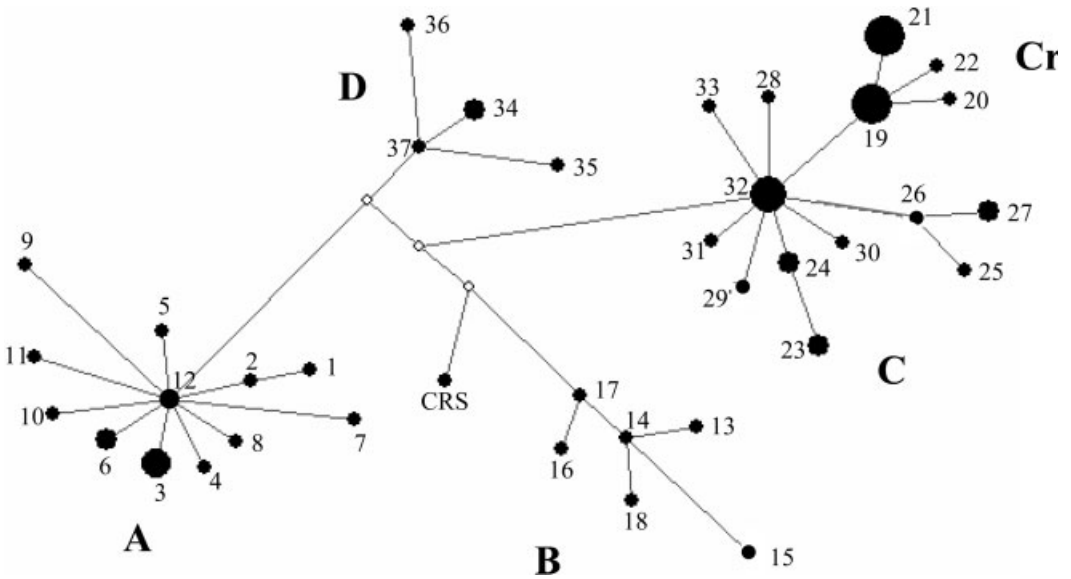

Fig. 3. Phylogenetic relationship of the 37 mtDNA HVS-I/II sequences shown in Fig. 2. Circle size is proportional to sequence frequency in the sample (CRS, Cambridge Reference Sequence).

lations examined (and corresponding to the founder C_1 sequence seen across the Americas). The other three revertant sequences represent one-step derivatives of sequence 19, with two of these (20 and 22) being restricted to one population (Piapoco, Guahibo) and one (21) being shared by three populations (Piapoco, Saliva, and Guahibo). The nucleotide diversity of the null RFLP haplotypes identified in the Colombian populations is 0.001, corresponding to about ¼ of the overall nucleotide diversity of haplogroup C in the Americas, consistent with the relatively recent origin of the reversion mutation.

Similar levels of population structure were observed in populations with or without the revertant C lineage as indicated by F_{st} values of ~8% (based on data for 7 classical markers; data not shown) and ~15% (using the mtDNA haplogroup frequencies of Table 1) for both population groups.

DISCUSSION

There is evidence in the literature that other populations from Northern South America could also carry the revertant C lineage identified here. A haplotype (AM83) identified in the Makiritare was reported by Torroni et al. (1993a) as lacking the haplogroup C-specific 13,259 *Hinc*II site loss and 13,262 *Alu*I site gain, but presenting the 10,397 *Alu*I site gain that characterizes super-haplogroup M (which includes haplogroup C and D, among others). Because haplotype AM83 also carries a 16049 *Rsa*I change that is shared by several haplogroup C haplotypes present in the Makiritare (and other Native populations), Torroni et al. (1993a) concluded that AM83 represented a revertant of haplogroup C. Unpublished sequence results cited in Schurr et al. (1999) appear to confirm this inference. Other mtDNA haplotypes with the 10,397 *Alu*I site gain but without the C or D-specific changes have been observed in both native populations from Eastern Colombia (Coreguaje, Sikuani, Murui, and Guayabero) and in admixed individuals from Colombia and Brasil (Keyeux et al., 2002; Rodas et al., 2003; Santos et al., 1999), suggesting that these populations are also likely to carry the C sublineage characterized here.

The identification of a revertant of the major founder haplogroup C in South America has implications for studies on the evolution of human populations in the region. Previous surveys of Native American mtDNA diversity have shown that most variation is population-specific, an observation

that has been interpreted as the result of population isolation soon after the initial settlement of the New World (Torroni et al., 1993a). Classical marker and Y-chromosome data also point to an ancient origin for many Native American populations (Bortolini et al., 2003; Thompson and Neel, 1996). The occurrence of genetic variants that are shared by several populations could therefore indicate that these mutations occurred at an early stage of the tribalization process or that they have been spread between populations by migration. The similar level of genetic structure observed with mtDNA and classical markers in populations with and without the revertant C lineage does not suggest a marked difference in migration rates between these population groups. Although a low level of migration contributing to the geographic dispersal of the C revertant lineage cannot be discounted, the genetic structure results are consistent with the C reversion mutation occurring early in the differentiation of the populations examined, followed by strong drift associated with population isolation. A more extensive analysis of the geographic distribution and molecular diversity of this revertant lineage should be highly informative for examining the microevolution of native populations in South America.

It has recently been suggested (Hunley and Long, 2005) that there is a weak relationship between Greenberg's linguistic classification (Greenberg, 1987; Ruhlen, 1991) and the genetic structure of North American Natives. More generally, it has been argued (Bolnick et al., 2004) that the linguistic classification for the Americas proposed by Greenberg should be abandoned in favor of the classification proposed by Campbell (1997). Criticism of Greenberg's classification includes a questioning of his multilateral comparison approach as a means of identifying a shared ancestry amongst languages. We note that of the five populations shown here to carry the revertant C lineage, four are included in Greenberg's Equatorial–Tucano linguistic family (Table 1), the Huitoto representing the only exception (this population being classified amongst the Ge-Pano-Carib). Furthermore, of the five other Native populations mentioned above as potentially carrying the revertant C lineage, three (Coreguaje, Sikuani, and Guayabero) are included in Greenberg's Equatorial–Tucano and two (Murui and Makiritare) among the Ge-Pano-Carib. Interestingly, the populations with highest frequency of the revertant C lineage are all in the Equatorial subfamily. These three populations (Guahibo, Saliva, and Piapoco) also share the derived revertant C sequence 21 (Fig. 2). By contrast, there is no apparent correlation between Campbell's linguistic classification and the population distribution of the revertant C lineage (Table 1). For example, Campbell's classification does not indicate a relationship between the languages spoken by the Guahibo, Saliva, and Piapoco, which show the highest frequency of the revertant C lineage (including the derived sequence 21). Thus, Greenberg's classification agrees with the data obtained here in pointing to similar ancestral connections between specific populations, despite an apparent high degree of genetic and linguistic differentiation between them. These results emphasize the need to collect larger genetic datasets in order to perform a more definite assessment of the relationship between linguistic classifications and patterns of genetic structure in the Americas.

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