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Molecular variability in Amerindians: widespread but uneven information*

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ABSTRACT

A review was made in relation to the molecular variability present in North, Central, and South American Indian populations. It involved results from ancient DNA, mitochondrial DNA in extant populations, HLA and other autosomal markers, X and Y chromosome variation, as well as data from parasitic viruses which could show coevolutionary changes. The questions considered were their origin, ways in which the early colonization of the continent took place, types and levels of the variability which developed, peculiarities of the Amerindian evolutionary processes, and eventual genetic heterogeneity which evolved in different geographical areas. Although much information is already available, it is highly heterogeneous in relation to populations and types of genetic systems investigated. Unfortunately, the present trend of favoring essentially applied research suggest that the situation will not basically improve in the future.

Key words: amerindians, genetic polymorphisms, population genetic variability, human microevolution.

INTRODUCTION

Human population genetics has a respectable past of almost 100 years; its root can be placed in the classical papers of Hardy and Weinberg, both published in 1908. In the 1940s and 1950s, the development of the synthetic theory of organic evolution successfully merged genetics with evolutionary biology, establishing the main factors which can be responsible for the intra and interpopulation genetic variability. In a parallel way, researchers interested in human polymorphic (normal, common) genetic markers expressed in blood started to compile and evaluate a vast amount of data at the world level, examples of which are the books by Mourant (1954), Mourant et al. (1958, 1976), Tills et al. (1983), Roychoudhury and Nei (1988), and Cavalli-Sforza et al. (1994).

Amerindians had been fairly well studied during all this period, and relatively recent reviews of their genetic variability and its evolutionary implications were performed by Salzano and Callegari-Jacques (1988) and Crawford (1998). These last studies, however, had been conducted when the amount of data at the molecular level was still scarce. Therefore, I decided to make a new global evaluation considering the variability in Amerindians that could be disclosed at this level. The results of this endeavor are presented below. Specific questions asked were: 1. From where in Asia did the first American colonizers originate? 2. How many waves of migration occurred, and at what time? 3. Do Amerindians present different levels and types of genetic variability, as compared to other ethnic groups? 4. Are there

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other peculiarities in the evolutionary processes that occurred in these populations? 5. Can significant genetic heterogeneity be found in different regions of the American continent?

ANCIENT DNA

The year 1984 was a turning point in the genetic study of organic compounds in ancient remains. In that year Higuchi et al. obtained the first successful amplification of ancient DNA (aDNA) from an extinct member of the horse family, the quagga. Soon afterwards, Pääbo (1985) reported the molecular cloning of aDNA from Egyptian mummies. The problem, however, was that at the time large amounts of aDNA were needed for these studies, so that only with the development of the revolutionary technique of polymerase chain reaction (PCR) they received new impetus (review in Herrmann and Hummel 1994).

As far as native Americans are concerned, a large number of papers appeared in succession (Doran et al. 1986, Pääbo et al. 1988, 1989, Pääbo 1989, Hauswirth et al. 1991, 1994, Rogan and Salvo 1994, Merriwether et al. 1994, Handt et al. 1996) emphasizing however many technical problems, especially the inability to amplify a significant number of samples and the contamination of samples with modern DNA (see extensive discussion in Kolman and Tuross 2000). Moreover, practically only mitochondrial DNA (mtDNA) could be obtained. 18S and 28S ribosomal RNA was studied by Rogan and Salvo (1994) from remains of seven individuals from Camarones, Morro, and Azapa, near Arica, northern Chile, but they concluded that the only nucleotide discrepancy observed from the 18S consensus could be artifactual. Similarly, dinucleotide markers could not be reliably typed from the remains of 28 individuals (including two Fueguian Indians) by Ramos et al. (1995b).

In a number of instances, however, reproducible results could be obtained for mtDNA, and in Table I 13 series composed of more than 10 individuals, and located all the way from the Aleutian islands to Tierra del Fuego, are presented. A total of 338 individuals had been studied, their remains being dated from 8,000 to 150 years before present. Wide variability in the frequencies of the classical Amerindian mtDNA haplogroups was found, with absence of haplogroups B and C among the past Aleuts; extensive intervals within the six USA series (A: 0-31; B: 12-73; C: 0-43; D: 0-55); predominance of the A haplogroup in the Amazon; and absence of A and B among the Dominican Republic and Fueguian-Patagonian remains. Since high frequencies of C and D are more common in South America, it is possible that the ancestors of the Taino migrated from South to Central America. The percentages of lineages that could not be classified in these four haplogroups were also quite variable, and reached as high a value as 69% at the Windower site.

Reports describing less than 10 individuals include: (a) Kolman and Tuross (2000), Plains region, west of USA, five skeletons, two B, two C, one undetermined; (b) Lleonart et al. (1999), Marien 2, Cuba, two skeletons, mother and child, both A; (c) Monsalve et al. (1996), eight Colombian mummies, five A, one B, two C; (d) Rogan and Salvo (1990), two mummies from Camarones, Azapa, Chile who did not present the 9 bp deletion, and therefore were non- B; and (e) Ramos et al. (1995b), bones and teeth from two Fueguian Indians, whose mtDNA was classified as belonging to haplogroups C and D, respectively.

Haplogroup X, that probably occurred in low frequencies among the Asian ancient colonizers of the Americas, has been found also in low prevalences in extanct North, but not South American Indians. As was emphasized by Ribeiro-dos-Santos et al. (1997), however, three of the non A-D haplogroups reported in their 1996 series could be classified as X.

All in all, the expectations that studies in ancient DNA could provide new insights in the Amerindian evolutionary histories have not yet been fulfilled. It is not clear whether the new mtDNA sequences observed in prehistoric skeletons and mummies belong to lineages previously present but now extinct, or are simple methodological artifacts.

TABLE I

Frequencies (%) of the main Amerindian mtDNA haplogroups obtained from ancient DNA material.

Archeological site or population	Antiquity (BP)	No. indiv. studied	mtDNA haplogroups (%)					Method	Refer.
			A	B	C	D	Others		
Aleut, Umnak and other islands	2,000-4,000	17	35	0	0	65	0	1	1
Pyramid Lake, Great Basin, USA	300-6,000	19	10	32	0	53	5	1	1
Stillwater Marsh, Great Basin, USA	300-6,000	22	5	36	0	55	4	1	1
Great Salt Lake, Fremont, USA	500-1,500	34	0	73	12	6	9	1	1,2
Anazasi, SW USA	1,010-2,010	22	23	59	9	0	9	1	1
Norris Farms Oneota, IL, USA	700	108	31	12	43	8	6	2	3
Windower, Central coast, FL, USA	7,000-8,000	16	0	12	0	19	69	3	4
Taino, La Caleta, Dominican Republic	1,680-670	24	0	0	75	25	0	2	5
Amazon Indians, Brazil	500-4,000	18	28	6	22	5	39	3	6
Aónikenk, Chile	150	15	0	0	27	73	0	4	7
Kawéskar, Chile	150	19	0	0	16	84	0	4	7
Selk'nam, Chile	150	13	0	0	46	46	8	4	7
Yámana, Chile	150	11	0	0	91	9	0	4	7

Methods: 1. Evaluation of four diagnostic sites, A: Hae III-663; B: 9 bp deletion; C: Hinc II-13259; D: Alu I-5176; 2. Four diagnostic sites plus sequencing; 3. Sequencing; 4. 9 bp deletion plus sequencing. References: 1. O'Rourke et al. (1996, 2000); 2. Parr et al. (1996); 3. Stone and Stoneking (1993, 1998, 1999); 4. Hauswirth et al. (1994); 5. Laloueza-Fox et al. (2001), 6. Ribeiro-dos-Santos et al. (1996); 7. Lalueza et al. (1993/94, 1997); Lalueza Fox (1996).

MITOCHONDRIAL DNA IN EXTANT POPULATIONS

Mitochondria are organelles found in the cell's cytoplasm. Their number and form vary depending on the function of the cell; a mammalian liver cell, for instance, harbors around 1,000 to 1,500 mitochondria. They are abundant in oocytes, but in sperm only four mitochondria, formed by the fusion of a larger number, are encountered at the neck of the sperm head; and they do not enter the oocyte at fertilization. Mitochondrial inheritance, therefore, is strictly maternal. Several evidences suggest that they originated as external micro-organisms which developed a symbiotic relationship with their host early in evolution. Their genome has 16,568 base pairs which are arranged in a circular fashion.

The earliest study that could be traced of the mitochondrial DNA (mtDNA) of Amerindians was one by Johnson et al. (1983). Using five restriction enzymes, which can cut the DNA (or not, depending on the nucleotide present in a given region), the types which could be established on this basis were investigated in 200 individuals from six different ethnic extraction, including 30 Warao Indians from Venezuela. The technique used is denominated restriction fragment length polymorphism (RFLP).

One of the co-authors of this paper was Douglas C. Wallace, who, after moving to the Emory University in Atlanta, USA, started a systematic evaluation of these polymorphisms in Amerindians. Initially six restriction enzymes were used (Wallace et al. 1985), but afterwards a set of 14 enzymes was employed (Torroni et al. 1992). Sequencing of the mtDNA control region were also utilized to investigate Amerindian population variability (Ward et al. 1991), and in many of the following papers the two techniques had been used (Torroni et al. 1993 and more recent papers).

Soon it was realized that, depending of the DNA construction in specific sites, the haplotypes (specific arrangements considering different combinations of results) and sequences could be grouped in four main sets (A, B, C, and D haplogroups), that

would have been present in the earlier colonizers of the Americas. Although this classification has been widely adopted among the researchers in this area, some investigators suggested that additional ones should be considered. For instance, Bailliet et al. (1994) divided each of the four in two subgroups according to whether restriction enzyme *Hae III* would or would not cut the DNA at position 16517; and the same group of researchers (Bianchi et al. 1995) suggested that not less than 13 founding haplotypes could be distinguished in Amerindians, combining RFLP and sequencing results.

A minor founding lineage, called haplogroup X, was also characterized by Brown et al. (1998). Unlike haplogroups A-D, haplogroup X is also found at low frequencies in modern European populations. Although the Amerindian and European variants are distinct, they are however distantly related to each other, and since haplogroup X has not been unambiguously identified in Asia the authors speculated that it could be an ancient link between Europe/Western Asia and North America. Thus far haplogroup X, although widely found in North American Indians (Smith et al. 1999), was not found in extanct South American natives, although it may have occurred in ancient populations of the region – see the previous section on ancient DNA. This problem is presently being extensively considered by our research group (Dornelles et al. 2000).

Since most of the Amerindian studies classified their findings on the basis of the classical four haplogroups, a general survey of the data should inevitably consider them. Table II presents a summary of these findings. A total of 90 samples, including 3,829 individuals, could be assembled. It is well established that Eskimo and Aleut populations arrived much later (4,500 years before present, or BP) than the Amerindians; and people who speak Na-Dene languages may also have arrived later (10,000-8,000 BP) than the remaining Amerindians, who would have crossed the Bering Strait circa 35,000 years BP (review in Crawford 1998; see below a further examination of this question). Therefore, the North American samples have been subdivided in these three sets for the present analysis.

As is shown in Table II, both the Aleut and Eskimo present basically haplogroups A and D. However, although in the only Aleut sample studied D is 2.4x as frequent as A, the opposite is true among the Eskimo (A 2.5x more common than D). Moreover, among the latter, there is a trend, with higher A frequencies in the north, which decrease as the D prevalences increase at southern latitudes. Among the Na-Dene the most marked characteristic is the high frequency of A, that in the Navajo and Apache occurs in association with lower B numbers. In the North American Amerind both A and D are more prevalent in the north, decreasing at southern latitudes. B is the most frequent haplogroup, 3.4x as frequent as D, but the four haplogroups are well represented.

In the Mexican and Central American samples, the majority has an absence of C and D. A is 1.9x as frequent as B; while in South America the most common haplotype is B, 1.7x as frequent as A. In this region there is a more uniform distribution of the four haplogroups (similarly to what happens in North American Amerinds). No clear geographical clines could be detected.

Mention was already made of divergent views about the number of haplogroups that would be present in the first American colonizers. Other questions that are still being debated today are those related to the number and time of the migration(s) into the Americas. Using measures of mtDNA diversity and other population genetic parameters Bonatto and Salzano (1997a, b) arrived at what they called the ''out of Beringia'' model of the continent's colonization. The picture suggested is that some time after Beringia had been peopled (60,000 to 11,000 years BP) the population expanded and crossed the Alberta ice-free corridor that connected this region to the south of North America or, alternatively, followed a coastal route. The collapse of ice sheets 14,000 to 20,000 years BP isolated Beringia from the rest of the continent during some time (2,000-6,000 years), and it was there that the Na-Dene and Eskimo diverged biologically. Amerind

TABLE II

Summary statistics on the mtDNA haplogroup frequencies observed in Native Americans.

Region and population	No. of samples[1]	No. of indiv.	Characteristic	mtDNA haplogroup frequencies				
				A	B	C	D	Others
North America								
Aleut	1	57	–	0.281	0	0	0.667	0.052
Eskimo	6	458	Minimum	0.261	0	0	0.033	0
			Maximum	0.967	0.024	0.078	0.642	0.122
			Average	0.653	0.004	0.020	0.267	0.056
Na-Dene	4	312	Minimum	0.517	0	0	0	0
			Maximum	0.966	0.414	0.138	0.069	0.056
			Average	0.758	0.146	0.047	0.026	0.023
Amerind	25	792	Minimum	0	0.056	0.028	0	0
			Maximum	0.667	0.909	0.461	0.412	0.375
			Average	0.246	0.363	0.212	0.106	0.073
Mexico and Central America	15	440	Minimum	0.214	0.037	0	0	0
			Maximum	0.850	0.714	0.484	0.259	0.062
			Average	0.573	0.297	0.094	0.029	0.007
South America	39	1770	Minimum	0	0	0	0	0
			Maximum	0.810	1.000	1.000	0.833	0.455
			Average	0.188	0.318	0.234	0.233	0.027

[1]Only sample sizes of 10 or more individuals were considered. – Sources: Torroni et al. (1992, 1993, 1994); Shields et al. (1993); Horai et al. (1993); Ginther et al. (1993); Santos et al. (1994); Bailliet et al. (1994); Merriwether et al. (1995, 1996, 2000); Batista et al. (1995); Kolman et al. (1995); Bianchi et al. (1995); Lorenz and Smith (1996); Santos (1996); Easton et al. (1996); Ward et al. (1996); Scozzari et al. (1997); Huoponen et al. (1997); Kolman and Bermingham (1997); Rickards et al. (1999); Mesa et al. (2000); Keyeux et al. (2001); unpublished data of S.L. Bonatto, F.M. Salzano et al.

differentiation occurred as the groups that were in North America migrated south. Therefore, there would have been just one major migration wave, which would have started 30,000-40,000 years BP.

An interesting situation is provided by the insertion of 540 bp of the mtDNA's control region into the nuclear genome. All populations studied thus far presented the insertion, suggesting that the event which led to its formation should have occurred after the separation of chimpanzees (which do not have it) and humans, but before the divergence of human populations. Frequency of the insertion is clinal, with low (10%-28%) values among Africans, intermediate (36%-65%) in Asia, Europe and the Pacific, but very high (54%-89%) in four Amerindian groups. This high interpopulation variability, and high heterozygosity levels within populations, make it a valuable tool for the investigation of human variation (Thomas et al. 1996).

Bortolini and Salzano (1996) performed an extensive analysis of the mtDNA variability of Amerindians, comparing it with those of other groups, and reached the following conclusions: (a) Total diversity, either considering characteristic haplogroups or a given set of haplotypes defined by 14 restriction enzymes, is of the same order of magnitude as those observed in other ethnic groups. Moreover, Amerindians present a degree of interpopulation variability that is higher than those found elsewhere; (b) Distinctive features were the low variability of the Na-Dene, and the high interpopulation diversity observed in Central Amerindians; and (c) The total diversity found in A, B, C, and D haplogroups is about one-third of that observed for the

African 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.

AUTOSOME MARKERS – HUMAN LEUKOCYTE ANTIGENS (HLA)

The HLA system in humans is the genetic region which corresponds, in other vertebrates, to their major histocompatibility complex (MHC). The corresponding antigens play an important role in the regulation of the immune response and can be divided into two groups: class I and class II molecules. Those of class I consist of an α chain and a β2-microglobulin, while class II molecules present noncovalently associated α and β chains. Both have an extracellular domain, a transmembrane portion, and a cytoplasmic tail.

The function of both sets of molecules is to collect peptide fragments inside the cell and transport them to the cell surface, where the peptide-HLA complex is surveyed by immune system T cells.

HLA variation can be investigated at different levels. In the earlier days the methods were basically serological, but with the advent of the molecular techniques a wide array of procedures were established which range from the study of specific sites by oligonucleotide hybridization to the sequencing of whole regions. As a result the genomic organization of the entire HLA region has been determined (MHC Sequencing Consortium 1999).

The extreme variability of the HLA system, as well as its physiologic importance, stimulated a large number of studies. Examples of evolutionary analyses which tried to establish the factors responsible for this variability are those of Ohta (1998, 2000), Gu and Nei (1999), and Meyer and Thomson (2001). A general evaluation of the population biology of HLA class I molecules, with special emphasis on Native American populations, was provided by Parham and Ohta (1996). As for class II loci, the papers by Erlich et al. (1997), Chen et al. (1999), Monsalve et al. (1999), Salamon et al. (1999), and Valdes et al. (1999) could be consulted. Two important characteristics of the system, not found in other gene complexes, are: (a) the inequivocal evidence of positive selection for several loci; and (b) the widespread generation of variability through interallelic gene conversion.

Previous reviews of the variability of the HLA system in Amerindians have disclosed interesting results. At the serological level Rothhammer et al. (1997), using principal-components analysis and synthetic gene frequency maps, observed longitudinal and latitudinal clines suggesting ancient migration routes. The molecular investigations, on the other hand, indicated: (a) a limited amount of polymorphism compared to other ethnic groups, confirming serological data (for instance, Fernández-Viña et al. 1997); (b) novel B locus variants, especially in South America (Cadavid and Watkins 1997); (c) the phenomenon of ''allele turnover'', that is, new alleles tend to supplant older alleles rather than supplementing them (Parham et al. 1997); and (d) an antigen-driven evolution of HLA-B molecules of Central and South American Indians aimed at generating novel peptide specificities not provided by the limited repertoire of founder allotypes postulated to have been present in the first migrants to the continent (Yagüe et al. 2000).

Three regions of HLA class II antigens produce functional antigen-presenting heterodimers; they are denominated DP, DQ, and DR. Each heterodimer is composed by the noncovalent association of two glycopeptide chains, α and β. For DQ two loci are usually recognized, DQA1 and DQB1. Tables III and IV present the information available on the variability of DPB1, DQA1, DQB1, and DRB1 in 61 Amerindian and Eskimo populations. For the four systems, there is far more information for South America than for Central or North America. The most studied system is DQA1, probably due to its use for forensic purposes. It was much more studied in North America (14 samples) than the other three (2-5 samples only). Three to seven alleles were observed in these surveys; **04* was generally the most common in North America, but not in Central or South America, where the most common allele was,

in the majority of the cases, **03*.

The most polymorphic system was DRB1, the number of alleles observed in the different surveys varying from 4 to 22 (averages in the three continents: 10-16). In this case, the allele that most often was present as the most common in North and South America was **1402*, but in three of the six Central American investigations the most frequent allele was **0407*.

The number of observed DQB1 alleles varied from 3 to 11 (averages: 5-9); **0301* occurred frequently in all three continents, but in South America an equally prevalent allele was **0302*. The latter was the most frequent in four of the six Central American studies. DPB1 also reveals several forms (2-12 alleles). In this case **0402* was the variant most often observed as the most frequent in the three regions.

Table V lists the class I A, B, and C variants which were discovered in Amerindians and are restricted to this ethnic group or derived populations. Locus B is by far the most variable (39 variants found there, against seven for the A and one for the C loci). Only a minority of them have arisen through point mutations (just four in 39, or 10% for the B locus, proportionally more for the other two), the vast majority having been formed through interlocus recombination or gene conversion. In terms of specificities or subtypes, variants of **02* were the most common in the A locus (5 in 7 or 71%), while B variants occurred in seven subtypes; **35* with 14 and **39* with nine accounted for more than half (59%) of the 39 B Amerindian mutations. The variants occurred most commonly in South America, where they were detected in 18 tribes or populations living in six countries (Venezuela, Colombia, Ecuador, Brazil, Argentina and Chile). Outside of South America, they were found in three identified groups from Mexico, one from Panama, and one from USA.

OTHER AUTOSOME MARKERS

There are at least five classes of genetic systems which can be investigated using molecular techniques, namely: (a) Short (for instance, *Alu*) or large (LINE) insertion polymorphisms; (b) Restriction fragment length polymorphisms (RFLPs); (c) Short tandem repeats (STRs), or microsatellites; (d) Single nucleotide polymorphisms (SNPs); and (e) Variable number of tandem repeats (VNTRs), also called minisatellites. On the other hand, our species possess twenty-two autosome chromosomes, and the number of Amerindian populations which can be studied is large. Unless a kind of global world project is developed to uniformly study a given set of populations with a standardized number of systems, heterogeneity of information is inevitable. It is, therefore, regrettable that the Human Genome Diversity Project received such a strong criticism of political activists that it could not develop appropriately.

Table VI presents the autosome DNA information available for Amerindians. There is no need to emphasize its heterogeneity. While some populations received considerable attention, the data from others are scanty. As was true for the other sets of data previously considered, geographical coverage is also uneven. Thus, while the table lists results concerning 58 South American samples, the numbers for North and Central America are respectively 26 and 7 only. They had been studied with different depth. The most studied North American groups were the Cheyenne, Maya and Navajo, while for the Mazatecan and Zuni populations information is available for one genetic system only.

Similar heterogeneity can be found in Central and South America (Table VI). Cabecar was the most studied group among the Central Amerindians, while the Suruí and Karitiana were the most thoroughly investigated in the south. The Arara, Gavião, Parakanã, Wai Wai, Xavante, and Zoró were also extensively studied in South America, although sometimes with different systems of markers.

It is impossible, here, to provide even a superficial global evaluation of all these populations and markers. Therefore, I will concentrate in some of the most recent reviews in which the Amerindians had been compared with other continental groups, giving also some examples of our own research.

TABLE III

Results concerning four Class II HLA polymorphisms in 61 Amerindian and Eskimo populations.

Population and region	No. of indiv.[1]	DPB1		DQA1		DQB1		DRB1		Refer.[2]
		No. alleles	Most common (%)	No. alleles	Most common (%)	No. alleles	Most common (%)	No. alleles	Most common (%)	
North America										
N.A. Indians 1	46	10	**0402* (30)	7	**03* (37)	10	**0301* (34)	20	**0407* (23)	3
N.A. Indians 2	199	ND	ND	6	**03* (38)	ND	ND	ND	ND	15
Eskimo, Greenland	42	ND	ND	5	**04* 49	ND	ND	ND	ND	15
Eskimo, USA 1	103	ND	ND	4	**04* (60)	ND	ND	ND	ND	15
Eskimo, USA 2	97	ND	ND	6	**04* (43)	ND	ND	ND	ND	15
Penutian	26	ND	ND	ND	ND	ND	ND	18	**1402* (35)	22
Athabascan	62	ND	ND	5	**0501* (48)	7	**0301* (45)	15	**1402* (35)	22
Tlingit 1	53	ND	ND	9	**0501* (59)	10	**0301* (65)	16	**1402* (52)	1
Tlingit 2	62	ND	ND	6	**04* (71)	ND	ND	ND	ND	15
Sioux 1	79	ND	ND	6	**03* (49)	ND	ND	ND	ND	15
Sioux 2	100	ND	ND	6	**03* (50)	ND	ND	ND	ND	15
Pueblo	103	ND	ND	6	**04* (76)	ND	ND	ND	ND	15
Navajo 1	81	ND	ND	5	**04* (71)	ND	ND	ND	ND	15
Navajo 2	74	ND	ND	4	**04* (77)	ND	ND	ND	ND	15
Zuni	50	4	**0402* (61)	3	**04* (77)	ND	ND	9	**1402* (32)	1,15
Central America										
Seri	100	ND	ND	5	**0301* (45)	5	**0302* (45)	7	**0407* (44)	16
Mazatecan	71	ND	ND	7	**03011* (48)	7	**0302* (48)	15	**0407* (28)	24
Zapoteco	75	12	**0402* (70)	6	**0301* (38)	11	**0301* (32)	15	**0802* (22)	16
Mixe	55	5	**0402* (91)	4	**0501* (44)	5	**0301* (41)	9	**1602* (31)	16

TABLE III (continuation)

Population and region	No. of indiv.[1]	DPB1		DQA1		DQB1		DRB1		Refer.[2]
		No. alleles	Most common (%)	No. alleles	Most common (%)	No. alleles	Most common (%)	No. alleles	Most common (%)	
Mixteco	103	10	**0402* (75)	5	**0301* (40)	10	**0302* (34)	15	**0407* (29)	16
Lacandon	162	ND	ND	4	**03* (76)	4	**0302* (77)	10	**0411* (47)	11
South America										
Yukpa	73	ND	ND	3	**0301* (77)	3	**0302* (76)	6	**0411* (62)	16
Bari	58	ND	ND	3	**03* (58)	3	**0302* (58)	6	**1602* (40)	4,8,11
Warao	72	ND	ND	3	**0501* (64)	3	**0301* (64)	4	**1602* (37)	11
Guahibo	54	6	**0402* (82)	4	**0501* (78)	8	**0301* (78)	8	**1402* (41)	12
Colombian I.1	21	ND	ND	ND	ND	ND	ND	11	**0407* (19)	13
Colombian I.2	217	11	**0402* (49)	6	**0301* (40)	8	**0302* (36)	19	**1402* (20)	17
Wayuu 1	54	3	**1401* (57)	ND	ND	ND	ND	ND	ND	10
Wayuu 2	56	ND	ND	7	**03* (45)	9	*0302 (42)	20	**1602* (14)	6
Wayuu 3	52	ND	ND	ND	ND	7	**0302* (48)	10	**0411* (27)	16
Arsario 1	50	2	**1401* (73)	ND	ND	ND	ND	ND	ND	10
Arsario 2	10	ND	ND	3	**03* (50)	3	**0302* (50)	4	**0407* (45)	6
Ijka 1	60	6	**0402* (57)	6	**0401* (63)	6	**0402* (63)	10	**0802* (62)	12
Ijka 2	62	ND	ND	7	**03* (45)	8	**0402* (41)	14	**0802* (41)	6
Kogui 1	60	3	**1401* (45)	3	**03* (72)	3	**0302* (72)	4	**1402* (17)	13
Kogui 2	34	ND	ND	4	**03* (67)	4	**0302* (63)	6	**0407* (55)	6
Tule	58	4	**0402* (53)	4	**03* (66)	4	**0301* (41)	10	**1402* (26)	12
Sikuani	60	4	**1401* (37)	3	*03 (75)	4	**0302* (78)	5	**0411* (47)	12
Waunana	60	5	**0402* (55)	3	**0501* (62)	4	**0301* (62)	9	**1602* (33)	12

TABLE III (continuation)

Population and region	No. of indiv.[1]	DPB1		DQA1		DQB1		DRB1		Refer.[2]
		No. alleles	Most common (%)	No. alleles	Most common (%)	No. alleles	Most common (%)	No. alleles	Most common (%)	
Embera	40	5	**1301* (35)	3	**0501* (56)	3	**0301* (58)	9	**1602* (33)	1,2
Nukak	40	3	**0301* (18)	3	**0501* (73)	3	**0301* (73)	5	**1402* (65)	12
Vaupes	46	2	**0402* (89)	ND	ND	ND	ND	ND	ND	10
Coreguaje	45	2	**1401* (52)	ND	ND	ND	ND	ND	ND	10
Ingano	22	5	**0402* **1401* (27)	3	**03* (59)	4	**0302* (55)	7	**0802* (36)	12
Cayapa	100	6	**1401* (49)	3	**0301* (56)	4	**0302* (41)	13	**0407* (27)	5,9
Quechua	108	ND	ND	6	**04* (49)	ND	ND	ND	ND	20
Ticuna	49	8	**0402* (43)	3	**03* (46)	5	**0302* (38)	9	**0411* (32)	21
Xavante	74	5	**0402* (80)	3	**0501* (61)	3	**0301* (61)	5	**1602* **1402* (30)	3
Terena	60	6	**0402* (47)	ND	ND	7	**0301* (58)	13	**1602* (27)	18
Guarani	92	7	**0402* (44)	7	**0501* (54)	7	**0301* (53)	5	**1602* (38)	19,23
Kaingang	108	7	**0402* (54)	5	**0401* (51)	5	**0402* (51)	6	**0802* (50)	19,23
Chiriguano	56	ND	ND	6	**0501* (61)	8	**0301* (59)	18	**1406* (19)	16
Mataco	60	5	**0402* (70)	ND	ND	ND	ND	ND	ND	2
Wichi 1	49	7	**0402* (62)	6	**0501* (46)	7	**0301* (48)	11	**1402* (26)	3
Wichi 2	48	6	**0402* (67)	ND	ND	ND	ND	7	**1402* (28)	14
Toba 1	135	12	**0402* (60)	7	**0501* (41)	9	**0301* (39)	22	**1406* (24)	3
Toba 2	124	7	**0402* (62)	ND	ND	ND	ND	10	**1406* (28)	14
Pilagá	19	8	**0402* (36)	6	**0501* (41)	6	**0301* (36)	11	**1406* (27)	3

TABLE III (continuation)

Population and region	No. of indiv.[1]	DPB1		DQA1		DQB1		DRB1		Refer.[2]
		No. alleles	Most common (%)	No. alleles	Most common (%)	No. alleles	Most common (%)	No. alleles	Most common (%)	
Kolla	60	ND	ND	ND	ND	5	**0302* (46)	5	**04* (42)	16
Chilean I.	43	ND	ND	ND	ND	ND	ND	15	**1402* (21)	13
Huilliche	40	ND	ND	ND	ND	ND	ND	9	**04* (27)	16

[1]Some variability occurs in the number of individuals sampled for the different loci. The number shown is the highest. – [2]References: 1. Imanishi et al. (1992); 2. Vullo et al. (1992); 3. Cerna et al. (1993); 4. Guédez et al. (1994); 5. Titus-Trachtenberg et al. (1994); 6. Yunis et al. (1994); 7. Garber et al. (1995); 8. Layrisse et al. (1995); 9. Trachtenberg et al. (1995); 10. Briceno et al. (1996); 11. Olivo et al. (1996); 12. Trachtenberg et al. (1996); 13. Blagitko et al. (1997); 14. Fernández-Viña et al. (1997); 15. Rivas et al. (1997); 16. Petzl-Erler et al. (1997); 17. Trachtenberg et al. (1998); 18. Lazaro et al. (1998); 19. Petzl-Erler (1998); 20. Gené et al. (1998); 21. Mack and Erlich (1998); 22. Monsalve et al. (1998); 23. Sotomaior et al. (1998); 24. Arnaiz-Villena et al. (2000). – Abbreviations: ND: Not determined; I: Indians.

In relation to the reviews, two basic approaches can be followed, one including a large set of markers, while the other concentrates in specific DNA regions. The first approach can be exemplified by three analyses: (a) Zhivotovsky et al. (2000) considered 72 STRs in 14 worldwide populations, which included the Maya, Karitiana, and Suruí. Through a statistical index of population expansion, introduced to detect historical changes in population size, they arrived to the conclusion that the Amerindians expanded their populations relatively late in relation to other continental groups, or that they have grown slowly, experimenting also a population bottleneck; (b) Jin et al.'s (2000) investigation involved 64 dinucleotide microsatellite repeats in 11 populations, including the Maya and Karitiana. Low variability in three parameters was obtained in these two groups, compared to the others; and (c) Deka et al. (1999) studied 23 microsatellite loci in 16 ethnically diverse populations, including the Dogrib, Cabecar and Pehuenche. In this case the coefficient of gene diversity was *higher* in Amerindians than elsewhere.

Two examples can also be singled out for the characterization of the second approach: (a) Four well-mapped SNPs spanning about 75 kb, two near each end of the phenylalanine hydroxylase (*PAH*) gene were selected to investigate linkage disequilibrium. A total of 29 populations, including the Karitiana, Suruí, and Ticuna, were studied. Disequilibrium between the opposite ends was significant in Native Americans and in one African population only. Distinctive haplotypes were observed between the Amerindians and other groups, including Eastern Asians (Kidd et al. 2000); and (b) Two STRs and a polymorphic *Alu* element spanning a 22-kb region of the plasminogen activator, tissue-type (*PLAT*) gene were considered by Tishkoff et al. (2000). Thirty human populations were surveyed, including the Cheyenne, Karitiana, Maya, Suruí, and Ticuna. In this DNA region the Amerindian pattern is not very different from those of other non-African populations.

The DNA results from our group have primarily concentrated in five tribes, the Tupi-Mondé-speaking Gavião, Suruí, and Zoró living in western Amazonia, the Gê-speaking Xavante of Central Brazil,

TABLE IV

Summary information of the data of Table III.

Sistems and characteristics considered	Continents		
	North America	Central America	South America
DPB1			
Sample sizes			
No. of samples	2	3	26
No. of individuals			
Range	46-50	55-103	19-217
Average	48	178	69
No. of alleles			
Range	4-10	5-12	2-12
Average	7	9	6
Most common alleles			
(no. of occurrences and average, %)			
**0301*	–	–	1,18
**0402*	2,45	3,79	18,58
**1301*	–	–	1,35
**1401*	–	–	7,49
DQA1			
Sample sizes			
No. of samples	14	6	27
No. of individuals			
Range	42-199	55-162	10-217
Average	82	94	68
No. of alleles			
Range	3-9	4-7	3-7
Average	6	5	4
Most common alleles			
(no. of occurrences and average, %)			
**03*	4,43	5,49	13,58
**04*	8,65	–	3,54
**05*	2,53	1,44	11,58
DQB1			
Sample sizes			
No. of samples	3	6	29

TABLE IV (continuation)

Sistems and characteristics considered	Continents		
	North America	Central America	South America
No. of individuals			
Range	46-62	55-162	10-217
Average	54	94	65
No. of alleles			
Range	7-10	4-11	3-9
Average	9	7	5
Most common alleles			
(no. of occurrences and average, %)			
**0301*	3,48	2,36	13,56
**0302*	–	4,51	13,54
**0402*	–	–	3,52
DRB1			
Sample sizes			
No. of samples	5	6	34
No. of individuals			
Range	26-62	55-162	10-217
Average	47	94	64
No. of alleles			
Range	9-20	7-15	4-22
Average	16	12	10
Most common alleles			
(no. of occurrences and average, %)			
**04*	–	–	2,34
**0407*	1,23	3,34	4,36
**0411*	–	1,47	4,42
**0802*	–	1,22	4,47
**1402*	4,38	–	9,30
**1406*	–	–	4,24
**1602*	–	1,31	8,31

TABLE V

Data on HLA A, B and C variants observed in Amerindians.

Variants	Population distribution	Molecular/physiologic characteristics	References
Locus A			
**0204*	Waorani	Generated by recombination, probably between *A*31012* and *A*2402*, leading to a G to T substitution at nt 362, and to the aa R97M change, exon 3	1,3
**0212*	Kaingang	Conversion from *A*2402* involving from two to 63 nt exchange	21
**0217*	Warao	Differs from *A*0204* at nt 355, G to T, leading to the aa change V95L, and A to T at nt 368, leading to the aa change Y99F, exon 3	14
**0219*	Terena, Toba, Wichi	Differs from *A*0201* by 7 nt substitutions and 5 aa changes	19,26
**0222*	Terena	Differs from *A*0201* at nt 196 (G to T), exon 3, leading to the aa L156W change	26
**6816*	Fueguian Indian	Differs from *A*68012* at codon 151, A to T, exon 3, leading to the aa change H151L and modifications in polarity and size	29
**6817*	Kolla	Differs from *A*68012* at nt 419, A to T, leading to the aa change D116V	30
Locus B			
**0807*	Ticuna, Yucpa	Differs from *B*0802* by a C to T substitution at codon 57, leading to aa change D57V	25
**1504*	Guarani, Waorani	Conversion from *B*51011* involving 16 to 92 nt exchanges	3,21
**1505*	"Native North American"	Differs from *B*6203* by aa changes E152V and W156L	5
**1507*	"Native North American"	Differs from *B*6203* by aa R97S change	5
**1508*	"Amerindian"	Differs from *B*1501* at three nucleotide positions, leading to aa E63N and S67F changes	7
**1520*	Kaingang	Recombination from *B*3501* involving 404 to 817 nt exchanges	6,21
**1522*	Bari, Cayapa	Originated from a recombination between the B15 and B35 groups of alleles at the middle of intron 2	11,12
**1541*	Nahua	Differs from *B*1501* by two base modifications (TG to CT), leading to aa change W156L	24
**3504*	Waorani	Generated by recombination, probably between *B*4801* and *B*52012*	3
**3505*	Guarani, Kaingang	Conversion from *B*4002* or *B*4801* involving 17 to 106 nt exchanges	4,21
**3506*	Kaingang	Conversion from *B*39011* involving 8 to 156 nt exchanges	4,21
**35091*	Mapuche	Differs from *B*3501* by three codons of the $\alpha 2$ domain	16
**35092*	Wichi	Differs from *B*3504* by three nucleotide differences	19
**3510*	Jaidukama	Differs from *B*3501* at codon 63 (A to G and C to G changes), leading to a N63E change at exon 2. As a consequence, a neutral polarity was transformed in a negative charge at this site	9
**3511*	Guarani	Conversion from *B*1501* or *B*51011*, involving 1 to 147 nt exchanges.	21
**3514*	Nahua	Differs from *B*3501* by three base changes, leading to aa V152Q and L156W modifications	15
**3516*	Nahua	Differs from *B*3501* by five-base differences and three aa substitutions	15
**3517*	Otomi	Differs from *B*3501* by three-base differences and two aa substitutions	18
**3518*	Toba, Pilagá	Differs from *B*3509* by two silent base changes and by a C to G substitutions at codon 156, leading to aa change R156L	19,22
**3519*	Pilagá, Toba, Wichi	Differs from *B*3501* in nt 133 (C to A) and 140 (C to G), exon 2; and by aa K45T change	19,26
**3520*	Terena	Differs from *B*3501* at nt 199 (C to T), exon 2; and by aa S67F change	26
**3521*	Terena	Differs from *B*3501* at nt 184 (A to T) and nt 240 (C to T), exon 3; and by aa V152E, Y171H modifications	26

TABLE V (continuation)

Variants	Population distribution	Molecular/physiologic characteristics	References
**39022*	Colombian Indian	Differs from *B*39021* by two silent substitutions, an A to G change at nt 246 and a T to C substitution at nt 1008, at exons 2 and 6, respectively	10
**3903*	Kaingang, Waorani	Conversion from *B*4002* or *B*4801* involving 1 to 70 nt exchanges	3,21
**3905*	Cayapa, Jaidukama, Kaingang, Mazatecan, Mexican, Toba, Yucpa	Differs from *B*39011* in codon 74, G to T, leading to the aa change D74Y, and a shift in peptide specificity	21,31
**39061,* **39062*	Bari, Mazatecan Otomi, Cayapa	They both differ from *B*3901* by five base differences, and one from another by a synonymous C to T change at codon 99	17,23
**3907*	Cayapa	Differs from all other *B*39* alleles by an A to G change at nt 69 and a T to C substitution at nt 76, leading to the aa changes N114D and F116S in exon 3	11
**3909*	Xavante, Warao, Yucpa	Differs from *B*3901* by the aa change Y99S. Peptide specificity and common natural ligands similar to B27	13,28
**3911*	Kuna	Differs from *B*3905* by a C to G substitution at nt 467, exon 3, leading to aa change L156R	20
**3912*	Terena	Differs from *B*3901* by one synonymous and two non-synonymous nt substitutions, leading to aa Y9D and S11A changes	26
**4004*	Guarani	Conversion from *B*3501* involving 27 to 114 nt exchanges	4,8,21
**4005*	Pima	Generated by recombination between *B*4002* and *B*5102*. It differs from *B*4002* by two aa changes, V152E and E163L	2
**4009*	Pilagá, Toba	Differs from *B*4002* at nt 66 (T to C) and 69 (G to A), exon 3; and by aa Y113H, D114N changes	19,26
**4802*	Waorani	Generated by recombination between *B*4801* and *B*3501*	3
**4803*	Pilagá, Toba, Wichi	Differs from *B*4801* at nt 20 (G to C), exon 3; and by aa S97R change	19,26
**5104*	Guarani	Conversion from *B*3501* involving 10 to 59 nt exchanges	4,21
**5110*	Kuna	Differs from other *B*51* alleles by a large change in at least 216 nucleotides	20
**5113*	Kolla	Differs from *B*51011* at nt 76 (A to T) and 92 (A to G), exon 3, leading to a synonymous and a non-synonimous (Y116F) changes	27
Locus C			
**1503*	Guarani	Point mutation from *Cw*1502*	21

References: 1. Castaño and López de Castro (1991); 2. Hildebrand et al. (1992); 3. Watkins et al. (1992); 4. Belich et al. (1992); 5. Choo et al. (1993); 6. Domena et al. (1994); 7. Hildebrand et al. (1994); 8. Adams et al. (1995b); 9. Gómez-Casado et al. (1995); 10. Adams et al. (1995a); 11. Garber et al. (1995); 12. Martinez-Laso et al. (1995); 13. Ramos et al. (1995a); 14. Selvakumar et al. (1995); 15. Vargas-Alarcón et al. (1996a,b); 16. Theiler et al. (1996); 17. Zhao et al. (1996); 18. Vargas-Alarcon et al. (1996c); 19. Fernández-Viña et al. (1997); 20. Iwanaga et al. (1997); 21. Parham et al. (1997); 22. Marcos et al. (1997); 23. Vargas-Alarcón et al. (1997); 24. Olivo-Díaz et al. (1998); 25. Mack and Erlich (1998); 26. Marcos et al. (1999); 27. Scott et al. (1999); 28. Yagüe et al. (1999); 29. Gómez-Casado et al. (2000); 30. Ramon et al. (2000); 31. Yagüe et al. (2000). – Abbreviations: aa: amino acid; nt: nucleotide.

TABLE VI

Autosome DNA information available for Amerindians.

Population	Systems	References
North America		
Alaska Natives	Eight *Alu* polymorphisms	1
Canadian Indians	NAD(P)H quinone oxidoreductase	2
Southwestern American Indians	DRD2 (Ser 311 Cys and Taq 1 RFLPs, intron-2 STR)	3
USA Native Americans	ADH2, ADH3, 9 STRs, 9VNTRs	4
Eskimo	Seven *Alu* polymorphisms, three subjected to sequencing, NAD(P)H quinone oxidoreductase, V_K A18	5
Carrier-Sekani	Angiotensin-converting enzyme (ACE), beta-fibrinogen, beta-globin (5 RFLPs), $beta_2$-adrenergic receptor	6
Cheyenne	ALDH2, CD4 STR and *Alu* deletion, delta ccr, DRD2, DRD4 VNTR, myotonic dystrophy CTG repeats, PLAT (STR/*Alu*), 33 dinucleotide loci of chromosome 20, 257 RFLPs, 20 STRs	7
Cree (see also Ojibwa)	D21S11, FGA, pyruvate carboxylase, 5 *Alu* polymorphisms	8
Dogrib	APO B 3' HVR, myotonic dystrophy CTG repeats, 23 STRs, 7 VNTRs, including D1S80	9
Huichol	4 STRs (CSF1P0, HPRTB, TH01, VWA), 2 VNTRs (APOB, D1S80)	10
Jemez Pueblo (see also Pueblo)	CD4 STR and *Alu* deletion, DRD2, DRD4 VNTR, myotonic dystrophy CTG repeats, PLAT *Alu* insertion	11
Maya	ADH2, ADH3, ALDH2, APOE (sequencing, haplotypes) CCR2-64I, CD4 STR and *Alu* deletion, CFTR, DRD2, DRD4 VNTR, HPA, LINE 1 (sequencing), mtDNA nuclear insertion, PLAT (STR/*Alu*), SDF1-3'A, 9 *Alu* polymorphisms, 30 RFLPs, 45 dinucleotides, chromosomes 9, 10, and 11, 64 dinucleotides, other chromosomes, 20 tetranucleotides	12
Mazatecans	APOE (RFLP)	13
Mic Mac	Pyruvate carboxylase	14
Mvskoke	Twenty two *Alu* polymorphisms, beta-globin (5 RFLPs), DRD4 VNTR, mtDNA nuclear insertion polymorphism	15
Navajo	ALDH2, ACE, APO, FXIIIB, PR, PV92 and TPA25 *Alu* polymorphisms, 33 dinucleotide repeat loci	16
Nu-Chah-Nulth	Beta-globin, MTHFR	17
Ojibwa (see also Cree)	D21S11, HUMFIBRA (FGA), pyruvate carboxylase	18
Pima	ALDH2, CD4 STR and *Alu* deletion, delta ccr5, DRD2, DRD4 VNTR, PLAT *Alu* insertion, 33 dinucleotide repeat loci, 20 STRs	19
Pueblo (see also Jemez Pueblo)	Cystic fibrosis (CFTR, 4 mutations), delta ccr5	20
Purepecha	4 STRs (CSF1PO, HPRTB, TH01, VWA), 2 VNTRs (APOB, D1S80)	10
Salish	D21S11, HUMFIBRA (FGA)	21
Sioux	ACE, APO, FXIIIB, PR, PV92, TPA25 *Alu* polymorphisms	22
Tarahumara	4 STRs (CSF1 PO, HPRTB, TH01, VWA), 2 VNTRs (APOB, D1S80)	10
Tlingit	Progesterone receptor (*Alu*)	23
Zuni	Cystic fibrosis R1162X mutation, 5 *Alu* polymorphisms	24
Central America		
Bribri	FV Leiden, FVHR2, FII20210G>A, MTHFRC>T	25
Cabecar	*Bgl II* site, PGK1 locus, myotonic dystrophy CTG repeats, 23 STRs	26
Chorotega	FV Leiden, FVHR2, FII20210G>A, MTHFRC>T	25
Emberá (see also South America)	CYP2D6, D6S366, D13S126, CSF1PO, F13A1, FESFPS, PLA2A1, TH01	27
Guaymi	*Bgl II* site, *PGK1* locus	28
Ngawbe	CYP2D6, 5 *Alu* polymorphisms	29
Wounan	D6S366, D13S126, CSF1PO, F13A1, FESFPS, PLA2A1, TH01, 5 *Alu* polymorphisms	30

TABLE VI (continuation)

Population	Systems	References
South America		
Brazilian Indians	Tetrahydrofolate reductase (MTHFR)	31
Colombian Indians	DRD4 VNTR	32
South Amerindians	ACE, APO, PV92, TPA25 *Alu* polymorphisms, 25 microsatellites	33
Aché	APOB signal peptide, LDLR 3' UTR (sequencing), 12 Alu insertions	34
Arara	ABO, APOB 3' HVR, APOE RFLP, beta-globin (6 RFLPs), D1S80, APOB, D4S43, VW1, VW2, F13A1, D12S67, Factor VIII (6 RFLPs), Factor IX (8RFLPs), HLA-F 5' UTR microsatellites, platelet HPA-1, HPA-2, HD, IL5R, SCA1, SCA3, TCRVB67, TCRVDJA, TNFA	35
Arrhuaco	ACE, APO, FXIIIB, PV92, TPA25 *Alu* polymorphisms	36
Arsario	C0L1A2, DAT1, D12S67, 9 STRs	37
Awá-Guajá	APOB, D1S80, D4S43, D12S67, F13A1, HD, HLA-F, HPA-1, HPA-2, IL5R, TCRVB87, TCRVDJA, TNFA, SCA1, SCA3, VWF1	38
Baniwa	APOE, delta ccr5, 5 *Alu* polymorphisms	39
Bari	D1S80	40
Cayapa	APOB, APOE, COL1A2 (3 RFLPs), MTHFRC>T	41
Chimila	ACE, α-globin 2, APO, FXIIIB, PV92, TPA25 *Alu* insertions, D1S80	42
Choreguaje	COL1A2, DAT-1, D12S67, 9 STRs	37
Doco	Progesterone receptor (PR) *Alu*	23
Emberá (see also Central America)	Beta-globin (5 RFLPs)	43
Gavião	APOB (3 RFLPs), APOE/APOC-I/APOC-II, LPL (3 RFLPs), beta-globin (5 RFLPs), CD4, F13A1, CYP1A1 (2 RFLPs), DRD2, DRD4, SLC6A3, D1S80, LDLR (5 RFLPs), LDLR 3' UTR (sequencing), TP53 (2 RFLPs, 1 duplication), von Willebrand (6 RFLPs)	44
Guambiano	5 *Alu* polymorphisms	45
Guarani	12 *Alu* insertions	46
Guayabero	5 Alu polymorphisms	45
Ijka	D12S67, 9 STRs	47
Inca	5 *Alu* polymorphisms	45
Ingano	Beta-globin (5 RFLPs), 5 Alu polymorphisms	48
Kaingang	12 *Alu* insertions, 20 STRs	49
Kamsa	Beta-globin (5 RFLPs)	50
Kanamari	Delta ccr5, 5 *Alu* polymorphisms	51
Karitiana	ACE, APO, FXIIIB, PR, PV92, TPA 25 *Alu* polymorphisms, 25 microsatellites, ALDH2, CD4 STR and *Alu* deletion, DRD2, DRD4 VNTR, LINE 1 (sequencing), myotonic dystrophy CTG repeats, PAH, PLAT (STR/*Alu*), SDF1-3' A, CCR2-64I, 64 dinucleotides, 30 RFLPs, 72 STRs	52
Kashinawa	Delta ccr5, 5 *Alu* polymorphisms	51
Katuena	APOB, D1S80, DYS43, D12S67, F13A1, HD, HLA-F, IL5R, TCRVB67, TCRVDJA, TNFA, SCA1, SCA3, VWF1	53
Kayapo (see also Xikrin)	ABO, APOB 3' HVR, APOE RFLP, beta-globin (6 RFLPs), D1S80, APOB, D4S43, F13A1, VWF VNTRs, Factor VIII (6 RFLPs), Factor IX (8 RFLPs), HLA-F 5' UTR microsatellites, platelet HPA-1, HPA-2, HD, IL5R, SCA1, SCA3, TCRVB67, TCRVDJA, TNFA	54
Kogui	COL1A2, DAT1, D12S67, 9 STRs, 5 *Alu* polymorphisms	55
Macushi	APOE	56
Makiritare	APOE	56
Mapuche	Beta-globin (5 RFLPs), CD4, CSF1P0, CYP1A1, CYP2D6, CYP2E1, D1S80, D2S44, D6S366, D7S820, D13S317, D16S539, FABP, FES/FPS, F13A1, HPRTB, RENA-4, TH01, VWA	57

TABLE VI (continuation)

Population	Systems	References
Mataco (see also Wichi)	APOB signal peptide, APOE RFLP, D1S80, FMR1 repeats	58
Paez	5 *Alu* polymorphisms	45
Parakanã	APOB, D1S80, D4S43, D12S67, F13A1, GSTM1 and GSTT1 deletions, HD, HLA-F, IL5R, TCRVB67, TCRVDJA, TNFA, SCA1, SCA3, spectrin alpha chain (α^{LELY}), VWF1	59
Pehuenche	APOB, D1S80, myotonic dystrophy CTG repeats, 23 STRs	60
Piaroa	CD4, F13A1 STRs	61
Pilagá	APOB signal peptide	62
Poturujara	HLA-F 5' UTR microsatellite	63
Quechua	ACE, APO, FXIIIB, PLAT, PR, PV92, TPA25 *Alu* polymorphisms, beta fibrinogen, beta2-adrenergic receptor, CD4 STR and *Alu* deletion, DRD4 VNTR, LINE 1 (sequencing), mtDNA nuclear insertion polymorphism, YNZ22, APOB, TH01, VW31A	64
Suruí	ALDH2, 5 *Alu* polymorphisms, APOB (3 RFLPs), APOE/APOC-I/APOC-II, LPL (3 RFLPs), beta-globin (5 RFLPs), CD4 STR and *Alu* deletion, F13A1, CFTR, CYP1A1 (2 RFLPs), D1S80, DRD2, DRD4, SCLCA3, D16S309 (MS 205) minisatellite, 64 dinucleotides, LDLR (5 RFLPs), LDLR 3' UTR (sequencing), 25 microsatellites, mtDNA nuclear insertion polymorphism, myotonic dystrophy CTG repeats, PAH, PLAT (STR/*Alu*), PR (*Alu*), 30 RFLPs, SDF1-3' A, CCR2-64I, 72 STRs, TP53 (2 RFLPs, 1 duplication), von Willebrand (6 RFLPs)	65
Tehuelche	CSF1P0, D6S366, D7S820, D13S317, D16S539, FABP, FES/FPS, F13A1, HPRTB, RENA-4, TH01, VWA	67
Ticuna	ALDH2, beta-globin (5 RFLPs), CD4 STR and *Alu* deletion, delta ccr5, DRD2, DRD4 VNTR, myotonic dystrophy CTG repeat, PAH, 6 *Alu* polymorphisms	66
Toba	APOB signal peptide, 5 *Alu* polymorphisms	68
Urubu-Kaapor	APOB, D1S80, D4S43, D12S67, F13A1, HD, HLA-F 5' UTR, IL5R, TCRVB67, TCRVDJA, TNFA, SCA1, SCA3, VWF1	69
Wapishana	APOE	56
Wayampi	APOB, APOE, beta-globin (6 RFLPs), D1S80, D4S43, VWF, Factor VIII (6 RFLPs), Factor IX (8 RFLPs), HPA-1, HPA-2	70
Wayana-Apalaí	APOB, APOE, beta-globin (6 RFLPs), D1S80, D4S43, VWF, Factor VIII (6 RFLPs), Factor IX (8 RFLPs), HPA-1, HPA-2	70
Wayuu	Beta-globin (5 RFLPs), D12S67, 6 *Alu* polymorphisms, 9 STRs	71
Wai Wai	APOB (3 RFLPs), APOE/APOC-I/APOC-II, LPL (3 RFLPs), beta globin (5 RFLPs), CD4, F13A1, CYP1A1 (2 RFLPs), D1S80, DRD2, DRD4, SLC6A3, HLA-F 5' UTR, LDLR (5 RFLPs), LDLR 3' UTR (sequencing), TP53 (2 RFLPs, 1 duplication), von Willebrand (6 RFLPs)	72
Wichi (see also Mataco)	CSF1P0, D6S366, D7S820, D13S317, D16S539, FABP, FES/FPS, F13A1, HPRTB, RENA-4, TH01, VWA	67
Xavante	12 *Alu* insertions, APOB (3 RFLPs), APOE/APOC-I/APOC-II, LPL (3 RFLPs), beta-globin (5 RFLPs), CD4, F13A1, CYP1A1 (2 RFLPs), D1S80, DRD2, DRD4, SLC6A3, LDLR (5 RFLPs), LDLR 3' UTR (sequencing), TP53 (2 RFLPs, 1 duplication), von Willebrand (6 RFLPs)	73
Xikrin (see also Kayapo)	D1S80, FcγIIa, IIIb, HPA	74
Yanomama	ABO, ACE *Alu*, APOA, APOB, APOE, APOH, beta-globin (6 RFLPs), D1S80, D4S43, VWF, Factor VIII (6 RFLPs), Factor IX (8 RFLPs), HPA-1, HPA-2, 4804 LR, 4815 LR	75
Zenu	Beta-globin (5 RFLPs)	76
Zoé	D1S80	77

TABLE VI (continuation)

Population	Systems	References
Zoró	APOB (3 RFLPs), APOE/APOC-I/APOC-II, LPL (3 RFLPs), beta-globin (5 RFLPs), CD4, F13A1, CYP1A1 (2 RFLPs), D1S80, DRD2, DRD4, SLC6A3, LDLR (5 RFLPs), LDLR 3' UTR (sequencing), TP53 (2 RFLPs, 1 duplication), von Willebrand (6 RFLPs)	78

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and the Carib-speaking Wai Wai who live farther north, near the Guiana border. A global analysis performed by Hutz et al. (1999) and involving eight autosomal DNA, mtDNA, and 23 blood group plus protein loci indicated that the autosomal DNA pattern of population relationships was exactly that expected according to history and geography, while the two other sets showed some departures from expectation.

Another type of comparison was made by Battilana et al. (2001), who studied 12 *Alu* polymorphisms, five of them never studied before in Amerindians, in four South American groups, two of the Tupi (Aché, Guarani) and two (Kaingang, Xavante) of the Gê linguistic families. The intertribal relations obtained with these polymorphisms were essentially the same as those found with 10 blood group + protein systems. The Aché, a Paraguayan tribe that only recently established more permanent contacts with non-Indians, clearly differentiated from the other three, showing, however, somewhat more similarity with the Guarani than with the Gê groups. This finding suggests that they may be a differentiated Guarani population that reverted or remained in the forests, and not a Gê group that preceded the Guarani colonization of Paraguay.

Considering the seven *Alu* polymorphisms studied by Battilana et al. (2001) for which there is comparative information in other Amerindians, the joint data are presented in Table VII. Again, the information available for South America is much larger than that obtained in North + Central America. Among the latter only TPA25 was studied in more than 500 individuals, while in South America

this number was reached for five of the seven loci. Average differences between the North + Central as compared to South America are small, in only one case (A25) exceeding the 10% value.

Fagundes et al. (2001) have sequenced 794 bp from the *Alu*-rich 3' untranslated region (3'-UTR) of the low density lipoprotein receptor (LDLR) gene from 102 chromosomes of a worldwide sample, about half of them derived from South American Indians. The region under study and its *Alu* U (upstream) repeat showed the highest mutation rates (0.56% per million years-Myr; 0.90% Myr) and nucleotide diversity (0.51% and 0.92%) ever found in nuclear sequences. Since the discrepant results obtained considering autosomal, mtDNA and Y chromosome data in relation to the origin and spread of modern humans may be related to differential rates of variation in these three sets, this region has a strong potential for evolutionary studies. The Amerindian data are compatible with a recent population bottleneck, as was previously suggested by mtDNA and Y chromosome studies, but not by other studies with autosomal DNA.

X AND Y CHROMOSOME VARIATION

Much less studies have been performed in the X than in the Y chromosome of Amerindians. As is indicated in Table VIII, while only nine systems had been investigated in the X, 66 were considered in the Y. The number of populations studied is also markedly different (nine for the X; 50 for the Y). As was true for other loci, South America was proportionally better investigated.

There is a simple explanation for the X/Y differences. The Y chromosome provides an unusual opportunity for the investigation of patrilineal lineages free of recombination, to be conveniently compared with the matrilineal lineages derived from the mtDNA. The X chromosome regions, on the other hand, present or exclusive inheritance that however is not free from recombination; or pseudoautosomal patterns in the homologous X/Y portion of them. Therefore, the dynamics of the process is not easily ascertainable.

The first Y chromosome findings which suggested almost no or very restricted variability were contradicted by more recent studies which documented more variation, although it is generally less marked than those found in the mtDNA or autosome regions. Several methods had been employed in these investigations, which included short tandem repeats (STRs), biallelic markers, or sequencing. To further complicate the matter, different arrays were utilized by different researchers (see the references in Table VIII), making comparisons among studies difficult.

Despite these shortcomings some generalizations are possible, as evidenced by most recent reviews. For instance, the suggestion of a single founding haplotype for the Americas (see, among others, Bianchi et al. 1997) has been substituted by the notion that at least two Y chromosome lineages contributed to the early peopling of the Americas (Rodriguez-Delfin et al. 1997, Karafet et al. 1999, Ruiz-Linares et al. 1999). As for their origin, Santos et al. (1999) suggested the central Siberian region as their possible parental land.

Bianchi et al. (1998) derived what they considered to be the ancestral founder haplotype, and dated its age as being of 22,770 years, in good agreement with mtDNA estimates. Carvalho-Silva et al. (1999), on the other hand, examined the low variability of the DYS19 microsatellite, as compared to those of five other tetranucleotide repeat loci. Factors such as relative position in the chromosome, base composition of the repeat motif and flanking regions, as well as degree of perfection and size (repeat number) of the variable blocks were considered. The only one that may be related to this low variability is small average number of repeats. Significant differences in variability using other markers were also observed between populations living in the Andean and non-Andean regions of South America (Tarazona-Santos et al. 2001).

Table IX shows data which exemplify the type of results that can be obtained using these markers. Haplotype distributions based on seven loci are presented, for comparisons involving North, Cen-

TABLE VII

Characteristics of previous studies involving seven *Alu* insertions performed in Amerindians.

Geographical region and statistical characteristics	Loci						
	FXIIIB	*MABDI*	*A25*	*TPA25*	*APO*	*PV92*	*ACE*
North + Central America							
No. of samples	10	2	2	16	10	10	10
No. of individuals	323	101	101	593	323	323	323
Lowest frequency	0.50	0.45	0.21	0.29	0.90	0.57	0.44
Highest frequency	1.00	0.46	0.21	0.66	1.00	0.99	0.89
Average	0.84	0.45	0.21	0.55	0.97	0.75	0.70
South America							
No. of samples	21	8	4	23	23	23	21
No. of individuals	840	454	179	810	856	876	695
Lowest frequency	0.53	0.42	0.01	0.12	0.58	0.42	0.54
Highest frequency	1.00	0.71	0.23	0.93	1.00	1.00	1.00
Average	0.90	0.54	0.07	0.55	0.97	0.86	0.78

Sources: Batzer et al. (1994); Barley et al. (1994); Tishkoff et al. (1996); Stoneking et al. (1997); Novick et al. (1998); Oliveira (1999); Rupert et al. (1999); Tishkoff et al.(2000); Battilana et al. (2002).

tral, and South American Indians. Haplotypes 5 to 7 occur in low frequencies, and since they present high prevalences in European or African populations, may be due to interethnic gene flow. The patterns of the other four are however more interesting. Haplotype 1, present in low frequencies in Asia only, is restricted to South America, and more specifically to two tribes of this region (Ticuna and Wayuu). Haplotypes 2 and 3 show opposite north-south gradients, while haplotype 4, common in Asians, has limited frequencies in the Americas.

HUMAN/MICROORGANISM COEVOLUTION

Several studies tried to relate microorganism variability with past Amerindian migrations. One example is the work of Agostini et al. (1997) on the human polyomavirus JC (JCV). They investigated its excretion in 68 Navaho and 25 Flathead Indians from USA. The large majority were of type 2A, consistent with the origin of these strains in Asia.

Much more detailed investigations had been conducted with the T-cell lymphotropic virus types I and II (HTLV-I, HTLV-II), especially with the latter. Examples are the papers by Neel et al. (1994), Black (1997), Miura et al. (1997), and Salemi et al. (1999). Since HTLV-II was present in high frequencies in American Indians, but not in Siberian ethnic groups, it was suggested that the first migrants to the New World should have been mainly from Mongolia and Manchuria. On the other hand, two HTLV-II subtypes, a and b, have been observed in Amerindians, and curiously, HTLV-IIa was found in Navajo populations of New Mexico and Kayapo groups of Central Brazil, but not in geographically intermediate communities.

OVERVIEW

It is clear that we presently have an enormous array of tools that could be used for the investigation of evolutionary processes in Amerindians or any other ethnic group. They differ in type of inheritance (lineal, maternal or paternal; recombina-

TABLE VIII

Information available on Amerindian X and Y chromosome genetic markers.

Chromosome and systems	Populations	References
X Chromosome		
DXS52, DXS548, DXS8174, DXS8175, DXYS156X, HUMARA [AGC]n, HUMHPRTB [AGAT]n, X-FRAXAC1, X-dys44	*North America:* Ojibwa, Seminole. *Central America:* Emberá, Kuna, Maya, Ngöbé, Wounan. *South America:* Aché, Arara, Guahibo, Karitiana, Kayapo, Wai Wai, Wayampi, Wayana-Apalai, Yanomama.	1-5
Y Chromosome		
αh, DXYS156Y, DYS1, DYS11 DYS19, DYS199, DYS257, DYS271 DYS287 (YAP), DYS388, DYS389A, DYS389B, DYS390, DYS391, DYS392, DYS393, DYS394, DYS395, DYS413, DYZ3, M3, M5, M7, M9, M15, M17, M19A, M45, M50, M88, M89, M95, M103, M110, M111, M119, M120, M122, M134, M911, polyAYAP, PN1, PN2, PN3, pSRY373, pYα1, RBF5 (T→C) (Tat), RPS4Y, SRY, SRY1532, SRY4064, SRY9138, SRY10831, SY81, YCAI, ICAII, YCAIIIA, YCAIIIB, 47z, 50f2, 92R7	*North America:* Cheyenne, Dogrib, Eskimo, Havasupai, Mvskoke Navajo, Ojibwa, Pima, Pueblo, Seminole, Sioux, Tanana, Zuni. *Central America:* Bribri, Cabecar, Emberá, Guaymi, Huetar, Kuna, Maya, Mixe, Mixtec, Ngöbé, Teribe, Wounan, Zapotec. *South America:* Aché, Arara, Arsario, Atacameño, Auca, Awá-Guajá, Ayoreo, Bari, Cayapa, Chimila, Chorote, Chulupi, Cinta Larga, Gavião, Guahibo, Guarani, Huilliche, Ijka, Ingano, Karitiana, Katuena, Kayapo, Kogui, Krahó, Lengua, Mapuche, Mocoví, Pacaás Novos, Parakanã, Pehuenche, Quechua, Suruí, Susque, Tehuelche, Ticuna, Toba, Urubu-Kaapor, Wai Wai, Warao, Wayampi, Wayana-Apalai, Wayuu, Wichi, Xavante, Yagua, Yanomama, Yupca, Zenu, Zoé, Zoró.	1-3, 6-40

References: 1. Zago et al. (1996); 2. Kolman and Bermingham (1997); 3. Scozzari et al. (1997b); 4. Zietkiewicz et al. (1997, 1998); 5. Mingroni-Netto et al. (2002); 6. Roewer et al. (1993); 7. Mathias et al. (1994); 8. Torroni et al. (1994); 9. Jobling and Tyler-Smith (1995); 10. Pena et al. (1995); 11. Santos et al. (1995a,b, 1996a,b,c, 1999); 12. Deka et al. (1996); 13. Hammer and Zegura (1996); 14. Mitchell (1996); 15. Ruiz-Linares et al. (1996, 1999); 16. Underhill et al. (1996, 1997); 17. Bianchi et al. (1997, 1998); 18. Hammer et al. (1997, 1998); 19. Huoponen et al. (1997); 20. Karafet et al. (1997, 1998, 1999); 21. Lell et al. (1997); 22. Rodriguez-Delfin et al. (1997); 23. Scozzari et al. (1997a,b); 24. Sherry and Batzer (1997); 25. Zerjal et al. (1997, 1999); 26. Bianchi et al. (1997, 1998); 27. Ruiz Narvaez (1998); 28. Santos (1998); 29. Carvalho-Silva et al. (1999); 30. Guarino et al. (1999); 31. Kittles et al. (1999); 32. Su et al. (1999b); 33. Vallinoto et al. (1999); 34. Bravi et al. (2000, 2001); 35. Forster et al. (2000); 36. Mesa et al. (2000); 37. Bortolini et al. (2001); 38. Kayser et al. (2001); 39. Ribeiro-dos-Santos et al. (2001); 40. Tarazona-Santos et al. (2001).

tional; based on extinct or extant material; involving not only the human, but also other genomes). Unfortunately, heterogeneity is the rule, not only in relation to the markers used, but also concerning the populations sampled. For instance, South America has been more thoroughly sampled than Central or North America. This may be due to the fact that populations were more diversified and intermixed less in the south than in northern latitudes. But other factors may be involved. Since field work involving humans is becoming increasingly difficult, and attempts to uniformize the data failed, this situation probably is not going to improve in the near future.

Answers to the questions posed in the intro-

TABLE IX

Y chromosome seven biallelic haplotype distribution observed in Native Americans[1].

Characteristics	North America			Central America	South America
	Eskimo-Aleut	Na-Dene	Amerind		
No. of samples	2	2	4	6	17
No. of individuals	66	68	122	110	356
Haplotype frequencies (averages, per cent)					
1	0	0	0	0	7
2	45	37	22	80	78
3	46	51	58	15	11
4	0	8	7	0	0
5	9	4	1	3	2
6	0	0	1	2	1
7	0	0	1	0	1

[1]The haplotypes are based in the genetic constitution present in the following sites: M19, DYS199, RPS4Y711, YAP, SY81, M9, 92R7, and were defined as follows: 1. ATC-AGT; 2. TTC-AGT; 3. TCC-AGT; 4. TCT-ACC; 5. TCC-ACC; 6. TCC+ACC; 7. TCC+GCC. – Source: Karafet et al. (1999); Bortolini et al. (2002).

duction can now be tried: 1. The original homeland of the first Amerindians remains elusive, different results having been obtained using mtDNA, autosomal, sex-chromosome, or viral parasitic information; 2. Different waves of migration had been postulated on the basis of mtDNA, Y chromosome, and other types of genetic and non-genetic (for instance, linguistic) evidences. The suggested dates of their occurrence are also variable; 3. The level of genetic variability of Amerindians, as compared to other groups, cannot be easily ascertained. There is restriction of variability for some of the mtDNA and HLA markers, but this is not necessarily so for other genetic traits. On the other hand, interpopulation variation seems to be more marked in Amerindians than elsewhere, probably due to their population structure; 4. The most exciting differences between Amerindians and non-Amerindians are those related to the HLA system, with the indication of allele turnover and antigen-driven positive selection especially at the B locus, probably due to historical processes of population changes in number, and to diversified exposure to infectious agents; 5. Certainly, many genetic differences could be detected along the continent. Some of them are clinal, while others are more abrupt. In a way this would be expected, due to the varied amount of population movements and of distinct environments they had to face.

Amerindians provide a good model for evolutionary studies due to many reasons: the date of their entrance in the continent is established within reasonable limits, and many studies had been undertaken among them that involved not only genetics, but other areas that are essential for evolutionary interpretations, such as demography, epidemiology and social anthropology. Let us hope that the present trend towards essentially applied investigations will not hamper further progress in the understanding of the past, present, and eventually future of this marvellous branch of humanity. But the perspectives certainly are not bright.

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RESUMO

Foi realizada uma revisão quanto à variabilidade molecular presente em populações indígenas das Américas do Norte, Central e do Sul. Ela envolveu resultados sobre DNA antigo, DNA mitocondrial em populações atuais, HLA e outros marcadores autossômicos, variação nos cromossomos X e Y, bem como dados de virus parasitas que podem mostrar mudanças coevolucionárias. As questões consideradas foram a sua origem, maneiras como ocorreu a colonização pré-histórica do continente, tipos e níveis da variabilidade que foi desenvolvida, peculiaridades dos processos evolucionários em ameríndios, e a eventual heterogeneidade genética que surgiu em diferentes áreas geográficas. Apesar de que já foi obtida muita informação, ela é muito heterogênea quanto a populações e tipos de sistemas genéticos investigados. Infelizmente, a tendência atual a favorecer pesquisas essencialmente aplicadas sugere que esta situação não deverá melhorar no futuro.

Palavras-chave: ameríndios, polimorfismos genéticos, variabilidade genética populacional, microevolução humana.

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