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Stable Human T-Cell Lymphotropic Virus Type 1 (HTLV-1) Subtype a/Subgroup A Endemicity in Amerindians From Northwest Argentina: A Health Problem to Be Resolved

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Jujuy province, in Northwest Argentina, is known to be endemic for HTLV-1 infection. Moreover, foci of HTLV-1 associated pathologies have also been described in this region. To gain an insight into the current situation of HTLV-1/2 in this endemic area, a seroprevalence and phylogenetic study was performed among a *Kolla* community from Abra Pampa city and surroundings. Out of 112 individuals, 11 (9.8%) were confirmed as HTLV-1 positive and no HTLV-2 infection was detected. The phylogenetic analysis of the LTR region showed that all the HTLV-1 sequences belonged to the Cosmopolitan subtype a/transcontinental subgroup A, and were closely related to reference sequences from Peru, Argentina, and the South of Brazil ($P = 0.82$). Considering the cultural and historical features of this community and in spite of the mandatory detection of anti-HTLV-1/2 antibodies in blood banks since 2005, it would be important to implement new public health measures focused on decreasing HTLV-1 transmission in this endemic area. ***J. Med. Virol. 82:2116–2122, 2010.***

KEY WORDS: HTLV-1/2; epidemiology; natives; phylogeny; northwest argentina

INTRODUCTION

Human T-cell lymphotropic virus type 1 (HTLV-1) was the first human retrovirus, discovered in 1980, isolated from a patient with cutaneous T-cell lymphoma [Poiesz et al., 1980]. Then, a second retrovirus named human T-lymphotropic virus type 2 (HTLV-2) was described in 1982, isolated from a patient with a variant form of a hairy T-cell leukemia [Kalyanaraman et al., 1982]. HTLV-1 is the etiological agent of a malignant disease called adult T-cell leukemia (ATL) [Poiesz et al., 1980] and a neurological disorder named HTLV-1 associated myelopathy/tropical spastic paraparesis (HAM/TSP) [Gessain et al., 1985]. Besides, immune-mediated diseases have also been associated with this infection [Morgan et al., 1989; Ijichi et al., 1990; LaGrenade et al., 1990; Mochizuki et al., 1992]. Although HTLV-2 was not initially associated with a specific disease, it is loosely correlated with rare neurological diseases resembling HAM/TSP or opportunistic infections, attributable to a compromised immune system [Modahl et al 1997; Murphy et al., 1997; Silva et al., 2002; Biglione et al., 2003]. Both retroviruses can be transmitted from mother-to-child by breast-feeding, as well as through sexual contact and contaminated blood products [Hino et al., 1985; Mueller, 1991].

Concerning molecular variability, seven subtypes have been identified within HTLV-1: Cosmopolitan (a), Central African (b and d), Melanesian (c), a variant from Zaire (e), one from Gabon (f) [Proietti et al., 2005], and one from Cameroon (g) [Wolfe et al., 2005]. The Cosmopolitan subtype, which is disseminated worldwide, is composed of five subgroups: Transcontinental

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(A), Japanese (B), West African (C), North African (D), and Black Peruvian (E) [Gasmi et al., 1994; Miura et al., 1994; Vidal et al., 1994; Van Dooren et al., 1998]. A lower variability has been observed within HTLV-2, which is composed of four subtypes: HTLV-2a, HTLV-2b, HTLV-2c, and HTLV-2d [Hall et al., 1992; Eiraku et al., 1996; Vandamme et al., 1998; Ishak et al., 2001].

HTLV-1/2 infections occur worldwide; however, they tend to be focally distributed, especially among local ethnic populations. For HTLV-1, there are areas of high endemicity such as Southern Japan, Intertropical Africa, the Caribbean, the Middle East, Melanesia, and South America [Proietti et al., 2005]. HTLV-2 is naturally endemic in some native populations from Africa and several aborigine communities of The Americas [Slattery et al., 1999]. An African origin has been suggested for these retroviruses, as the result of multiple episodes of simian-to-human transmissions [Van Dooren et al., 2001]. Later, several "out-of-Africa" migrations have contributed to HTLV-1/2 dissemination worldwide, and thus these viruses are nowadays found endemically or sporadically in most human populations. In the Americas, an ethnic/geographic restriction of the infection has been observed being HTLV-1 detected in natives of the highlands from Venezuela, Colombia, Peru, Bolivia, and Chile and HTLV-2 among Amerindians from the lowlands of Venezuela, Colombia, Paraguay, and Brazil [Slattery et al., 1999; Carneiro-Proietti et al 2002].

In Argentina, there is an HTLV-1 endemic area in the Northwest (*Kolla* ethnic group) and an HTLV-2 endemic focus in the Gran Chaco region (*Wichi* and *Toba* ethnic groups) [Biglione et al., 1999, 2003; Dipierri et al., 1999; Fujiyoshi et al., 1999].

To gain an insight into the current epidemiology of HTLV-1/2 among *Kolla* individuals from Northwest Argentina, the seroepidemiology of these two infections were studied. In addition, the phylogenetic analysis of positive samples was carried out aimed to characterize HTLV-1/2 genotypes that are present in this endemic area.

MATERIALS AND METHODS

General Characteristics of the Study Population

Abra Pampa, one of the main cities of the Puna Jujeña region, is located in the Northwest of Argentina, 215 km North of San Salvador de Jujuy, the capital city of Jujuy province. Most of Jujuy inhabitants are *Kolla*, living dispersed in the Puna Jujeña and in the gorge of Humahuaca. The *Kollas* are considered the second most numerous ethnic group of Argentina, composed of 53,019 inhabitants, dispersed in the Northern provinces of Salta and Jujuy, all of them characterized by a strong autochthonous genetic component. Abra Pampa is inhabited mostly by *Kolla* individuals who maintain the cultural and social costumes with an estimated population of 9,425 (INDEC, 2004). This city has a primary health care center that offers a very basic service. Although public health services are available in this city and HTLV-1/2 testing can be performed, the poor economical situation of most people living in Abra Pampa and surroundings makes it difficult even to access to public hospitals.

Recruitment Procedure and Ethical Approval

During August 2007, people older than 18 years were invited to participate in the study through a radio communication, in which professionals, involved in this project explained the objectives and scopes of the study. After hearing the radio communication, people who had interest to participate attended a health center situated in Abra Pampa in a specific date and time. First of all, a personal interview with health staff was carried out. Then, they were invited to sign an informed consent and after that the blood extraction was performed. Epidemiological data of the study population was obtained by a standardized questionnaire. All participants were of *Kolla* ethnic origin, living in Abra Pampa city and surroundings. After performing HTLV-1/2 diagnosis, infected individuals were then counseled and referred for medical follow-up at the local health center.

This study was reviewed by the institutional review boards and Scientific Ethical Committee at the University of Buenos Aires and conducted in compliance with all federal regulations governing the protection of human subjects (OHRP reference numbers: IORG #0004063 and IRB#00004817).

HTLV-1/2 Diagnosis

Blood samples were collected in Vacutainer tubes with EDTA solution (Becton Dickinson, Argentina SRL) and plasma was obtained after blood centrifugation (1,900 rpm, 10 min). HTLV-1/2 antibody screening was performed by commercial ELISA (Murex, HTLV-1 + 2; Murex Diagnostics, Dartford, England) and by a particle agglutination (PA; SERODIA-HTLV-I; Fujirebio, Tokyo, Japan). Reactive samples were confirmed by Western Blot (WB; HTLV blot 2.4; Genelabs Diagnostics, Science Park, Singapore).

DNA was extracted from buffy coats using the QIAamp DNA extraction kit (QIAGEN, Hilden, Germany). A β-actin PCR was performed in order to check the quality of the extracted DNA. Indeterminate samples were further confirmed by amplification of *tax* and *pol* genes with a specific "in-house" nested-PCR [Heneine et al., 1992; Tuke et al., 1992]. To perform the phylogenetic characterization, the 3′-LTR region (528-bp, ATK-1 genome position 8196–8699) was amplified by a hemi-nested PCR [Meertens et al., 2001]. Hemi-nested PCR products were then purified using a commercial extraction kit from agarose gel and sequenced in an ABI Prism 3100 Genetic Analyzer according to the manufacturers' instructions.

Phylogenetic Analysis

Sequence alignment was carried out by using Clustal W (BioEdit 7.0.4.1 sequence alignment editor) [Hall,

1999], including the sequences reported in this study and 96 HTLV-1 reference genotypes previously described. An STLV-1 sequence (Gene Bank Accession Number NC_000858) was used as outgroup. Once aligned, the data set consisted of sequences spanning 401-pb. Phylogenetic analyses were performed with the MrBayes program [Huelsenbeck and Ronquist, 2001; Ronquist and Huelsenbeck, 2003], which was run on a computer cluster using four processors per run. Eight Markov Chain Monte Carlo processes were run for 5×10^6 generations, sampling the posterior distribution of trees every 500 generations.

The MrBayes analyses were run independently twice, and Metropolis coupled Markov Chain Monte Carlo was used to enhance the tree-climbing capabilities of the Markov chains [Huelsenbeck and Ronquist, 2001]. We used eight incrementally heated Markov chains, using the default heating function of MrBayes. Every 10th generation, 10 attempts were made to swap states between pairs of chains picked at random. The effective sample sizes (ESS) of the estimated parameters were obtained with the Tracer program [Rambaut and Drummond, 2007]. Posterior probabilities were calculated on a 50% majority rule consensus tree of the post-burn-in sample (burn in = 500). The nucleotide evolutionary model (GTR) was inferred by the MrAIC.pl script [Nylander, 2004]. Adequate mixing and convergence were assessed by the Tracer program [Rambaut and Drummond, 2007]. The tree topology was visualized with TreeView (http://taxonomy.zoology.gla.ac.uk/rod/treeview.html).

RESULTS

Epidemiological Data of the Study Population

This study included 112 samples from natives born and living in Abra Pampa city, Jujuy province and surroundings. The median age of the studied individuals was 48-years old (Interquartile range: 33.25–58.75). Of them, 93 (83%; 95% CI: 75.6–90.4) were female and 19 (17%; 95% CI: 9.6–24.4) male. Considering familial risk antecedents for HTLV-1 associated pathologies, 4 (3.6%; 95% CI: 1–8.9) of them reported neurological disorders with signs of spasticity in low limbs and impairments for walking, and 1 (0.9%; 95% CI: 0.02–4.9) reported maternal antecedents of leukemia. Regarding the clinical features of participants, 8 (7.1%; 95% CI: 1.9–12.4) manifested problems in low limbs and difficulty in walking, and 1 (0.9%; 95% CI: 0.02–4.9) a previous non-Hodgkin Lymphoma. Twelve (10.7%; 95% CI: 4.5–16.9) of them had been transfused in health centers in the Puna Jujeña region. No other risk factors for HTLV-1/2 infection were found. Out of the total, 76 (67.9%; 95% CI: 58.8–76.9) individuals had children. When people were asked about their previous knowledge about HTLV-1/2 infection, only 7 (6.3%; 95% CI: 1.3–12.2) participants (all of them HTLV-1/2 negatives) answered to have heard about it, as a sexually transmitted infection similar to Human Immunodeficiency Virus.

HTLV-1/2 Diagnosis

Screening procedure of all 112 plasma samples showed that 11 (9.8%; 95% CI: 3.9–15.8) of them were confirmed as HTLV-1 (showing a complete profile of HTLV-1 proteins) by WB. One sample (J3), exhibiting an indeterminate WB pattern (rgp-46-1 protein), was then confirmed as negative by hemi nested-PCR. Out of 11 HTLV-1 positive samples, 1 (J49) resulted repeatedly negative for β-actin by PCR, and therefore it was excluded from the phylogenetic analysis. No HTLV-2 positive samples were detected.

Epidemiological Data of HTLV-1 Positive Individuals

When prevalence by gender was studied, three (15.8%; 95% CI: 3.4–39.6) individuals were men and eight (8.6%; 95% CI: 2.4–14.9) female, being these rates not significantly different ($P > 0.05$). The median age was 51-years old (Interquartile range: 33.75–59.75). Six HTLV-1 positive individuals reported to have one or more children. Regarding familial relationship, two individuals (J78 and J79) were sisters, and both reported to have been long breast-fed. One participant (J20) reported difficulty to walk and familial antecedents of paraparesis (Table I). None of them had been previously transfused with blood components.

Phylogenetic Studies

Out of the total, 3′-LTR region from 10 samples were successfully amplified by hemi-nested PCR. To construct a comprehensive phylogenetic dataset, sequences reported here were aligned along with 96 HTLV-1 reference sequences obtained from the Genebank database, preferentially chosen from neighboring countries and those previously reported in South American countries. The phylogenetic reconstruction was performed by using the Bayesian method. The plotting of the log-likelihood scores against generation times, indicated that the two independent runs, which started from random trees, reached stationary at equivalent average log-likelihoods (first run: mean = −2236.9279, median = −2236.35; second run: mean = −2236.2608, median = −2235.737). The ESS were >300, and the standard deviation of splits frequencies was <0.005. The phylogenetic tree obtained by this approach is shown in Figure 1. The topology showed that all subtypes (a, b, c, d, e, and f) were clearly obtained, with good statistical support ($P \geq 0.81$). Moreover, within the Cosmopolitan Subtype all known subgroups, Transcontinental ($P = 1.00$), Japanese ($P = 0.66$), West African/Caribbean ($P = 0.52$), North African ($P = 0.95$), Black Peruvian ($P = 0.79$), and a separate clade reported before [Van Dooren et al., 2004] and then confirmed and named as *Divergent* by our group [Eirin et al., 2008] could also be distinguished.

All the studied sequences were nested into HTLV-1 a/Transcontinental subgroup A, clustering within a previously described *Big Latin American clade* which

TABLE I. Epidemiological Features of the 11 HTLV-1 Infected Individuals From a *Kolla* Population of the Northwest Argentina

Sample ID	Gender	Age (years)	Birth place (town)	Children (n)	Clinical symptoms related to HTLV-1 associated diseases	Familial antecedents for HTLV-1 associated diseases
J20	F	49	Agua Caliente	1	Disable to walk	Father with paraparesis in low limbs
J37	M	58	Abra Pampa	0	—	—
J43	M	48	Puerta de Potrero	1	—	—
J47	F	59	Tabladitas	0	—	—
J49[b]	M	80	Puerta de Potrero	0	—	—
J68	F	60	Abra Pampa	0	—	—
J73	F	63	Casabindo	1	—	—
J74	F	52	Miraflores	7	—	—
J77	F	50	Rinconada	6	—	—
J78*	F	29	Cienaga grande	2	—	—
J79**	F	19	Mina Pirquitas	0	—	—

*Samples that have reported familial relationship. In particular, Samples J78 and J79 belonged to two sisters.
**Sample J49, removed from phylogenetic study for being β-actin repeatedly negative and the indeterminate J3 sample confirmed as negative by *pol*/*tax* nested PCR.

included sequences from Peru (Me1, Me2, Qu1, Qu2, and Qu3); Southern Brazil (MASU, BRRJ122-97 MAQS, FCR, BRRJFA and BRRJ86-97) and Argentina (Ar5, Ar15, Ar49, Neu1, Neu11, BD12; PW1 and FSW3; Fig. 1, $P = 0.82$) [Van Dooren et al., 1998; Eirin et al., 2008].

Within this *Latin American group*, eight sequences from *Kollas* (J20, J43, J68, J73, J74, and J77–79) were closely related to each other, and grouped with two Argentinean references (Ar15 and Ar49), both from Amerindians of the Northwest endemic region (Fig. 1, *subcluster 1*, $P = 0.68$). Four of these sequences (J43, J77–79) showed strong similarity to each other and were included in a well-supported clade (Fig. 1, *subcluster* 2, $P = 0.98$). Two sequences from *Kollas* (J37 and J47) seem to be more distantly related to the other new sequences, branching off from the monophyletic *subcluster 1*.

Sequence similarity analysis including the new Argentinean and prototype strains showed the highest one to the HTLV-1a prototype ATK-1 (96.96%; 95% CI 96.7–97), followed by HTLV-1d (95.2%; 95% CI 95–95.4), HTLV-1e (94.2%; 95% CI 94–94.4), HTLV-1 f (93.3%; 95% CI 93–93.6), HTLV-1b (93.2%; 95% CI 93–93.4), and HTLV-1c (90.9%; 95% CI 90.6–91.2). Moreover, the similarity percentage obtained among the studied samples and every prototype was significantly different (one-way ANOVA, $P < 0.001$).

Comparison of the 401-bp fragment among the studied sequences showed that they differed in fourteen positions with respect to the ATK-1 prototype, being nine of them observed in all 10 sequences: mutations A8367C, A8403G, G8446A, A8509G, T8546C, C8606G, and C8616A; an insertion of one adenine at position 8429; and a deletion of one adenine at position 8510.

The remaining five changes were detected in some sequences as follows: G8391A in J47; G8393A in J43; T8488C in J37, J43, J68, J73, J74, J77–79; C8489G in J43, J77–79 and G8653A in J73. Moreover, we compared the nucleotide sequences of samples J78 and J79, finding that they were identical along all the 401-bp analyzed (100% similarity).

DISCUSSION

This study describes the seroepidemiology and the genetic characterization of HTLV-1 genotypes in an aboriginal community living in Northwest Argentina, an endemic area for HTLV-1 infection. Previous studies conducted in South America including this country have described the prevalence of HTLV-1 infection ranging from 0.8% to 6.8% in Aymara communities from the Andes highlands (Peru, Bolivia, and Chile). On the other hand, HTLV-2 infection prevalence ranges from 1.4% to 57.9% among lowlands Amerindians from Brazil, Paraguay, Chile, and Argentina [Fujiyoshi et al., 1999]. In this study, a high rate of HTLV-1 infection (9.8%) is reported among *Kollas* while HTLV-2 infection has not been detected, confirming the outstanding ethnic/geographic restriction of HTLV-1 and HTLV-2 infections and corroborate that the *Kolla* community from the Puna Jujeña region integrates the Northern Andean natural geographical clustering of HTLV-1 [Dipierri et al., 1999; Fujiyoshi et al., 1999].

Regarding previous HTLV-1/2 seroprevalence studies among *kollas* in the same area, only one report was performed [Dipierri et al., 1999]. When comparing the seroprevalence by gender of both studies, no significant differences were observed in females ($P > 0.05$). Nevertheless, the prevalence was 3.8-fold higher than that reported in 1999, suggesting an increasing trend for HTLV-1 infection in this group. Maybe, the absence of significant differences could be attributed to a reduced statistical power due to the sample size. On the other hand, in this study the HTLV-1 infection was detected in men (15.8%; 95% CI: 3.4–39.6) in comparison to the previous data, in which this infection had not been described in this group.

Concerning phylogeny, the Cosmopolitan subtype/Transcontinental subgroup A has been observed as

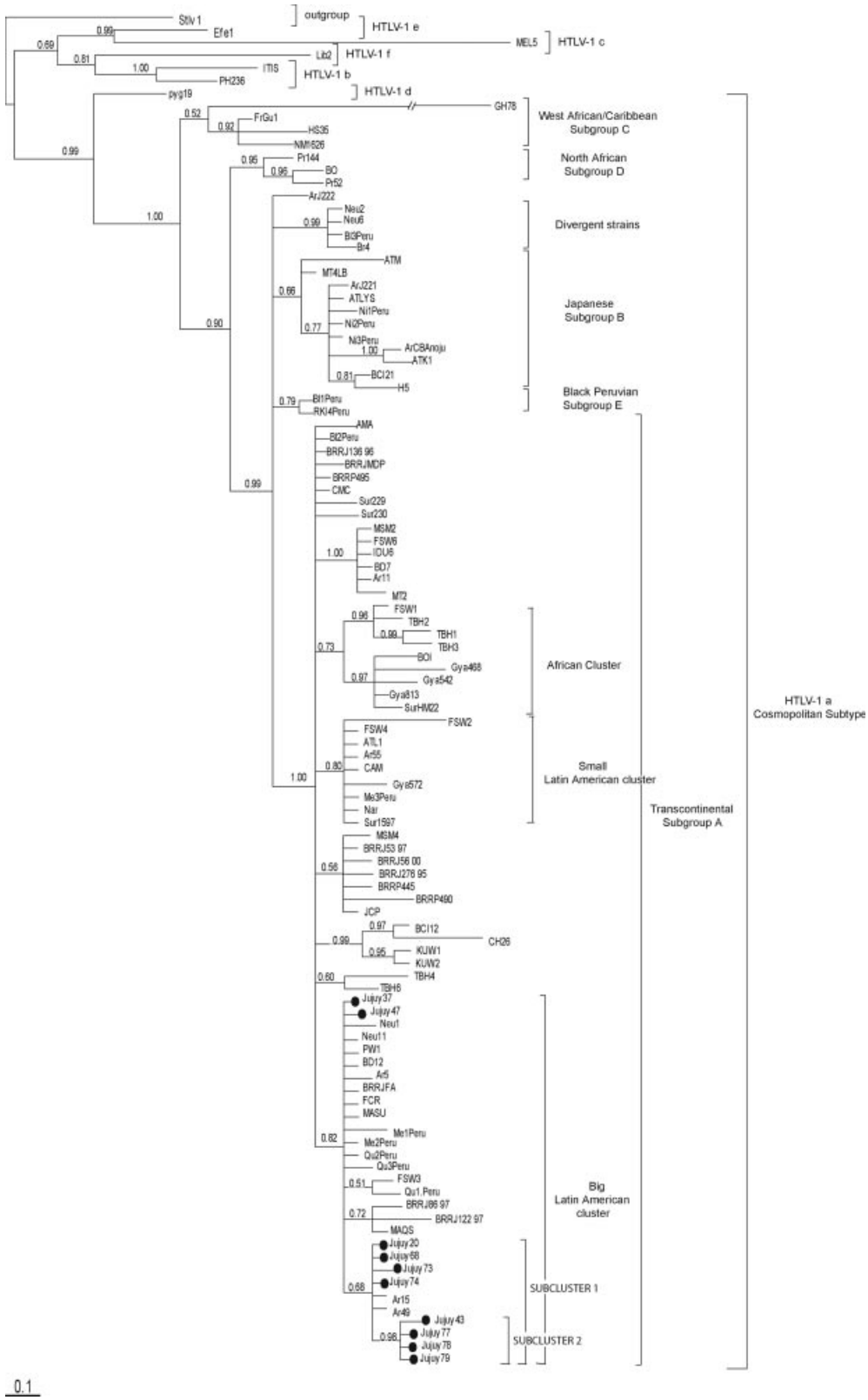

Fig. 1. Bayesian phylogenetic tree obtained from a 401-bp fragment of the 3′-LTR region of 105 HTLV-1 strains including 10 Kollas from Northwest Argentina. Eight Markov Chain Monte Carlo processes were run for 5×10^6 generations, sampling the posterior distribution of trees every 500 generations. Posterior probabilities were calculated on a 50% majority rule consensus tree of the post-burn-in sample (burn in = 500). Numbers above branches indicate posterior probabilities. The sequences described in this study (closed circles) have GeneBank accession numbers FJ751854 to FJ751863.

the major subgroup among native descendants in the Northwest region of Argentina, though the Japanese subgroup B has recently been described in two native individuals from Jujuy [Van Dooren et al., 1998; Gastaldello et al., 2008]. In this study, the only presence of the Transcontinental subgroup A among *Kollas* has been detected confirming this subgroup as predominant.

The majority of the sequences described in this paper grouped in a tight cluster (*subcluster 1*) with two references (Ar15 and Ar49) of Amerindian origin from Jujuy, suggesting that these genotypes share a common origin and revealing the presence of a highly stable geographical retrovirus variant in this area. Interestingly, two out of 10 *Kolla* sequences described in this paper branched off the *subcluster 1*, showing some degree of molecular diversity of the HTLV-1 in this community.

Regarding the origin of HTLV-1 genotypes introduced in South America, the new sequences did not cluster with Transcontinental references from Africa (TBH1–TBH3) and from South American countries with an important African ethnic component (as the result of the slave trade) such as Guyana (Gya468, Gya542, Gya572, and Gya813), Suriname (Sur229-230, SurHM22, and Sur1597), and Brazil (BRRJ5397, BRRP445, and BRRJMDP). On the other hand, *Kolla* sequences grouped in a *Big Latin American cluster* with references from Peruvian Mestizo (Me1, Me2.Peru) whose mitochondrial DNA showed them as Amerindian descendants; Peruvian Amerindians (Qu1-Qu3) and from Brazilian references previously described as White (MASU, BRRJ122–97), black (MAQS, FCR) and non-white, including mulatos and black (BRRJFA and BRRJ86–97) ethnic background individuals. Furthermore, sequences from Argentina reported before were also present in this monophyletic *Big Latin American group,* belonging to Amerindians from the North (Ar5, Ar15, and Ar49); one from a female sex worker from Salta city, in Northwest Argentina (FSW3) and from Buenos Aires residents that had been born in Peru (Neu1, Neu11, and BD12) and Bolivia (PW1) [Van Dooren et al., 1998; Eirin et al., 2008] (Fig. 1, $P = 0.82$). These data confirm a common geographical origin of all genotypes, integrating an Andean natural cluster of HTLV-1 [Dipierri et al., 1999].

Regarding the endogamy, it is reasonable to understand the maintenance of the virus strains over the years and their closer relationship observed in the phylogenetic analysis (Fig. 1, *subcluster 1*). Besides, a prolonged breast-feeding is common in this community, which is considered the main route for HTLV-1/2 infection to the offspring. In this study, in two cases (J78 y J79) the vertical transmission way is considered, suggesting a common origin of the virus. These samples belonged to two young sisters of 19- and 29-years old respectively, who reported to have been long breast-fed. In addition, the analysis of their provirus sequences revealed that they did not differ in their nucleotide composition along the 401-bp analyzed. Considering this fact, a previous study performed with vertical transmission chains for HTLV-1 infection, including families of Argentinean Amerindians from the Northwest, showed a remarkably stability of the retrovirus for the LTR region and a positive correlation between the occurrence of mutations and the age of the individual infected [Van Dooren et al., 2004]. Taking this into account, one would not expect to find differences in the LTR sequences.

Although it could be important to extend the study to a larger group, these results provide an update of the epidemiology of this infection and show evidence of deficient public health education of this community in the endemic HTLV-1 Puna Jujeña region. It is interesting to emphasize that only 6.3% of all participants, all HTLV-1/2 negative, answered to have heard about this retrovirus previously, suggesting a lack of information about HTLV-1 among this community, residing in a known endemic area for this infection. Thus, this result indicates that it would be important to implement new public health policies adapted to this particular population, focused to prevent the dissemination of this virus and other infections.

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