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Endemic Infection With HTLV-IIB in Venezuelan Indians: Molecular Characterization

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Summary: The peripheral blood of 41 Yaruro and Guahibo Indians from Venezuela was examined for HTLV antibodies and DNA. Twenty-five samples (61%) were found to be infected with HTLV-IIB. The sensitivities of the serologic and DNA polymerase chain reaction (PCR) analyses were 80% and 96%, respectively. Epidemiologic studies supported both sexual and perinatal transmission of the virus. Sequence analyses of the HTLV-IIB strains from these Indians indicate that they are unique relative to HTLV-II detected in other groups of humans. HTLV-IIB-G2 isolated from a Guahibo Indian is the most divergent HTLV-IIB strain relative to the prototype HTLV-II NRA. **Key Words:** HTLV-IIB—Endemic infection—Venezuelan Indians.

HTLV-I and HTLV-II belong to a group of oncogenic retroviruses (1,2). HTLV-I is associated with a variety of clinical disorders, including T-cell lymphomas and leukemias, neurodegenerative disease, polymyositis, arthritis, and uveitis (1,3–5). HTLV-II has been increasingly associated with rare lymphocytic neoplasms and cases of neurodegenerative disease (2,6–9).

HTLV-I and HTLV-II are ~60% homologous at the genetic level (10,11). Two major subtypes of HTLV-I exist, African and Austronesian, which are about 90% homologous to each other, and 2 major subtypes of HTLV-II, A and B, which are about 94% homologous to each other (12–15). Most North Americans infected with HTLV-II, including intravenous drug users in whom the virus is endemic, are infected with subtype A, whereas most Paleo-Amerindians from Florida, Central America, and South America are infected with subtype B (12–20). Interestingly, the Kayapo Indians of Brazil are infected with a variant of subtype A (21,22) and HTLV-II is endemic among some African pygmy groups (23).

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Recently, we have shown that HTLV-II is endemic among some, but not all, Venezuelan Amerindians (24–26). We wanted to identify the particular HTLV-II subtype or subtypes prevalent in these groups and to compare the performance of various serologic and nucleic acid techniques in the detection of HTLV-II infection. We also wished to follow-up on initial epidemiologic studies regarding transmission of HTLV-II among these people and to identify both infected and uninfected individuals for prospective clinical evaluations.

MATERIAL AND METHODS

Study Populations

The Indian populations studied, the Guahibo and the Yaruro, inhabit two small communities in Venezuela separated by approximately 500 km (Fig. 1). The Guahibo and Yaruro languages have been linked with the Arawak and the Paleo-Chibchan linguistic trees, respectively (27,28). Members of these communities rarely mix with other ethnic groups. The Yaruro still obtain their food mainly by means of fishing, hunting, and gathering, but the Guahibo recently started to work in cotton plantations. No evidence of drug abuse or recent blood transfusions has been documented in these individuals. All babies are breast fed but wet nurses are not used. Polygamy is practiced by the Yaruro (29).

Previous studies (24,25) indicated that the prevalence rate of HTLV-

FIG. 1. Map of Venezuela showing the location of the Guahibo and Yaruro communities.

II infection among the Guahibo and Yaruro were 25% and 6%, respectively. In the investigations described herein, we returned to study family members of previously identified positive individuals.

Peripheral blood samples from 100 HTLV-I/II–seronegative North American volunteer blood donors (NAVBD) were used as controls.

Collection and Processing of Blood Specimens

The Yaruro (24) were sampled in 1993 in the Venezualan Apure state, whereas the Guahibo (25) blood samples were obtained in 1996 in Bolivar state (Fig. 1). In both cases, heparinized and clotted blood samples were drawn after obtaining oral consent from each individual through an interpreter. Basic data including name, age, gender, race, family relationships, and birth place were collected by interviewing competent adults. Both sera and peripheral blood mononuclear cells, isolated by Ficoll-Hypaque (Pharmacia, Piscataway, NJ, U.S.A.) density gradient centrifugation, were frozen.

Serology

Sera from 17 Guahibo subjects were screened for antibodies to HTLV-I/II by two commercial enzyme-linked immunosorbent assays (ELISA) (Cambridge Biotech, Worcester, MA; Organon-Teknika, Durham, NC, U.S.A.). Sera that were repeatedly reactive by at least one ELISA test were deemed to be positive. All samples were tested by HTLV-I/II Western blot (WB) spiked with rgp21e (Cambridge Biotech) and by an indirect immunofluorescence assay (IFA) against HTLV-I– and HTLV-II–transformed cell lines (MT2 and clone 19, respectively), as previously described (24). Sera from the 24 Yaruro subjects were similarly analyzed but, in addition to these tests, ELISA-positive samples were also analyzed in radioimmunoprecipitation assays (RIPA) (24). Positivity was assigned according to the Association of State and Territorial Public Health Laboratory Directors (ASTPHLD) criteria (30).

Polymerase Chain Reaction and Sequence Analyses

DNA was organically extracted as previously described (14). Samples were first determined to contain amplifiable DNA by performing polymerase chain reaction (PCR) with the human β-globin primers PCO_3 and PCO_4 (31). One microgram of each DNA sample was amplified with the HTLV-I/II *pol* primers SK110/SK111 for 60 cycles of PCR. Specific detection of HTLV-I or HTLV-II sequences was performed using a commercial assay (Cellular Products, Buffalo, NY, U.S.A.) (32). Samples were also amplified with the HTLV-II–specific long terminal repeat (LTR) primers HTIIL (26–47) +/HTIIL (624-606)-, and the amplified products were detected by Southern blot hybridization using oligonucleotide HTIIL (351-329)+d (14). Samples were scored as PCR-positive if the signal intensity of both the *pol* and the LTR hybridizations were greater than or equal to that of the 10-copy positive control. If sufficient DNA was available, samples were also amplified with the HTLV-I/II tax primers HTIIpX(7248-7267)+/HTIIpX(7406-3886)- and the HTLV-II–specific *env* primers HTIIE(5799-5818)+/HTIIE(6125-6106)- and the amplified DNAs were detected with the probes HTIIpX(7337-7376)+d and HTIIE(6047-6064)+d, respectively (14). All pre- and post-PCR reactions were done by separate personnel in separate buildings and all *pol* PCR reactions were done with diuridine triphosphate (dUTP) instead of thymidine triphosphate (TTP) and presterilized with uracil *N*-glycosylase to prevent carryover contamination.

HTLV-II *pol* sequences were subtyped as either A or B by oligomer restriction analysis of amplified DNA using the enzymes *HindI* or *MseI* as previously described (19). Amplified LTR DNAs from the G-2, G-4, Y-5, and Y13 strains; amplified *pol* DNA from the G-2 strain; amplified *tax* DNA from the G-2, G-3, Y-5, and Y4 strains; and amplified *env* DNA from the G- 2, G-4, and Y-14 strains were cloned and sequenced as described (14). Sequences were aligned (33) and the neighbor joining method utilizing the maximum likelihood technique to determine distance matrices (34) was used to compare new and previously published HTLV-II LTR sequences (20). Both distance and bootstrap (100 replications) trees were generated.

RESULTS

Serology

Eleven Yaruro and nine Guahibo samples were defined as HTLV-II–seropositive. All 20 ELISA- and WB-positive specimens were also positive when tested by IFA with both MT2 and clone 19 cell lines. When IFA end points were determined by fourfold serial dilutions, all samples tested exhibited at least a fourfold higher titer against the clone 19 cell line, consistent with HTLV-II infection (data not shown). The 11 Yaruro seropositive samples were also positive using RIPA.

Polymerase Chain Reaction and Phylogenetic Analyses

All 100 DNA samples from HTLV-I/II–seronegative NAVBD were positive for human β-globin but negative for HTLV-I and HTLV-II DNA. All 41 Venezuelan Indian DNA samples were positive for human β-globin and all were negative for HTLV-I *pol* DNA. Twenty-four samples were positive for both HTLV-II *pol* and LTR DNAs (14 Yaruro and 10 Guahibo samples). When these samples were also tested for HTLV-II *tax* and *env* DNA, they were also positive. Two samples, Y-4 and G-4, were positive for *LTR* or *pol*, but not both. Y-4 was also tested

for *tax* and was positive and G-4 was tested for *env* and was found negative. These samples were both seronegative, and their positive PCR results were consistent with a copy number between 10 and 100 (data not shown). For the purposes of our further analyses, these two samples were deemed PCR-negative. Among the 20 seropositive samples, 19 (95%) were PCR-positive. Among the 24 PCR-positive samples, 19 (79%) were seropositive. If all seropositive and PCR-positive samples are considered true-positives, then the sensitivities of the serologic and PCR analyses were 80% and 96%, respectively, (p = .09, Fisher's exact t-test). The specificities of the tests, including those performed on the NAVBD, were 100%.

Amplified HTLV-II *pol* DNA from 10 infected Indian samples belonging to both ethnic groups were subtyped as B by oligomer restriction analysis (data not shown). All HTLV-II sequences (Gen Bank accession numbers AF005393-AF0015403) obtained from the 6 Indians tested (3 Yaruro and 3 Guahibo) were consistent with their being of the B subtype (Fig. 2; data not shown). Phylogenetic analyses of the 556 bases of LTR from the HTLV-II G2 and Y5 strains show that they are distinct from each other and from all other published HTLV-II strains (Figs. 2 and 3) and belong to the HTLV-IIB subtype. Relative to the prototype isolate NRA, G-2 is the most divergent HTLV-IIB strain identified to date.

HTLV-II Prevalence and Transmission

When data from both Indian groups are combined, the prevalence of HTLV-II infection in these positive families was 25 out of 41 (61%). The mean age of the infected male Indians was 38 years (range, 14–90 years), whereas the mean age of the female Indians was 33 years (range, 2–70 years), which was not significantly different. The prevalence in male Indians was 9 of 16 (56%) and in female Indians was 16 of 25 (64%) (p = .43, Fisher's exact t-test). In Indians >20 years of age, the prevalence in male Indians was 9 of 13 (67%) and in female Indians was 13 of 18 (72%) (p = .58, Fisher's exact t-test). In both genders, among individuals >20 years of age, the prevalence was 22 of 31 (71%), and for

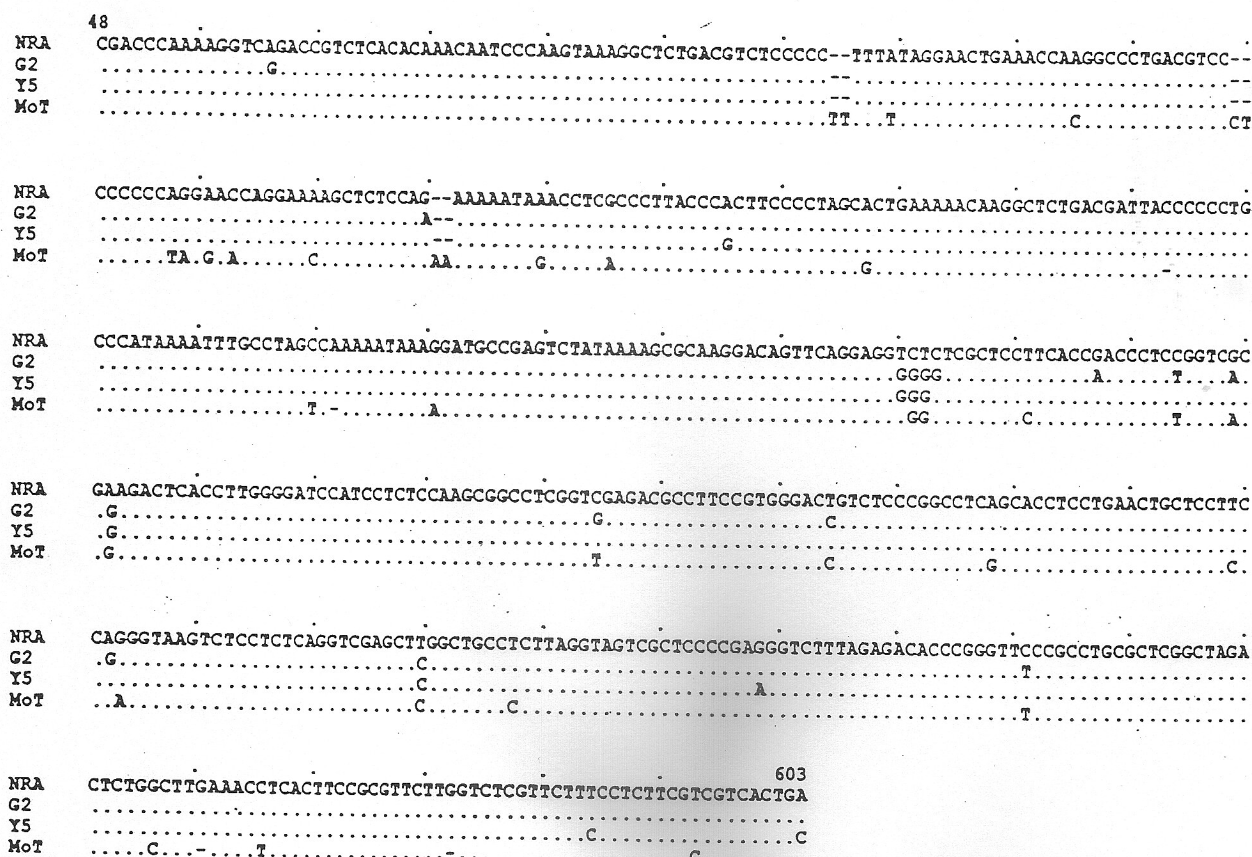

FIG. 2. Alignment of 556 bases of the HTLV-II long terminal repeat. The sequence for the prototypic HTLV-IIB strain NRA is shown, as are the base changes in the Venezuelan strains G-2 and Y-5 and the prototypic HTLV-IIA strain MoT. Conserved sequences are represented by a ·, and deletions are represented by a –.

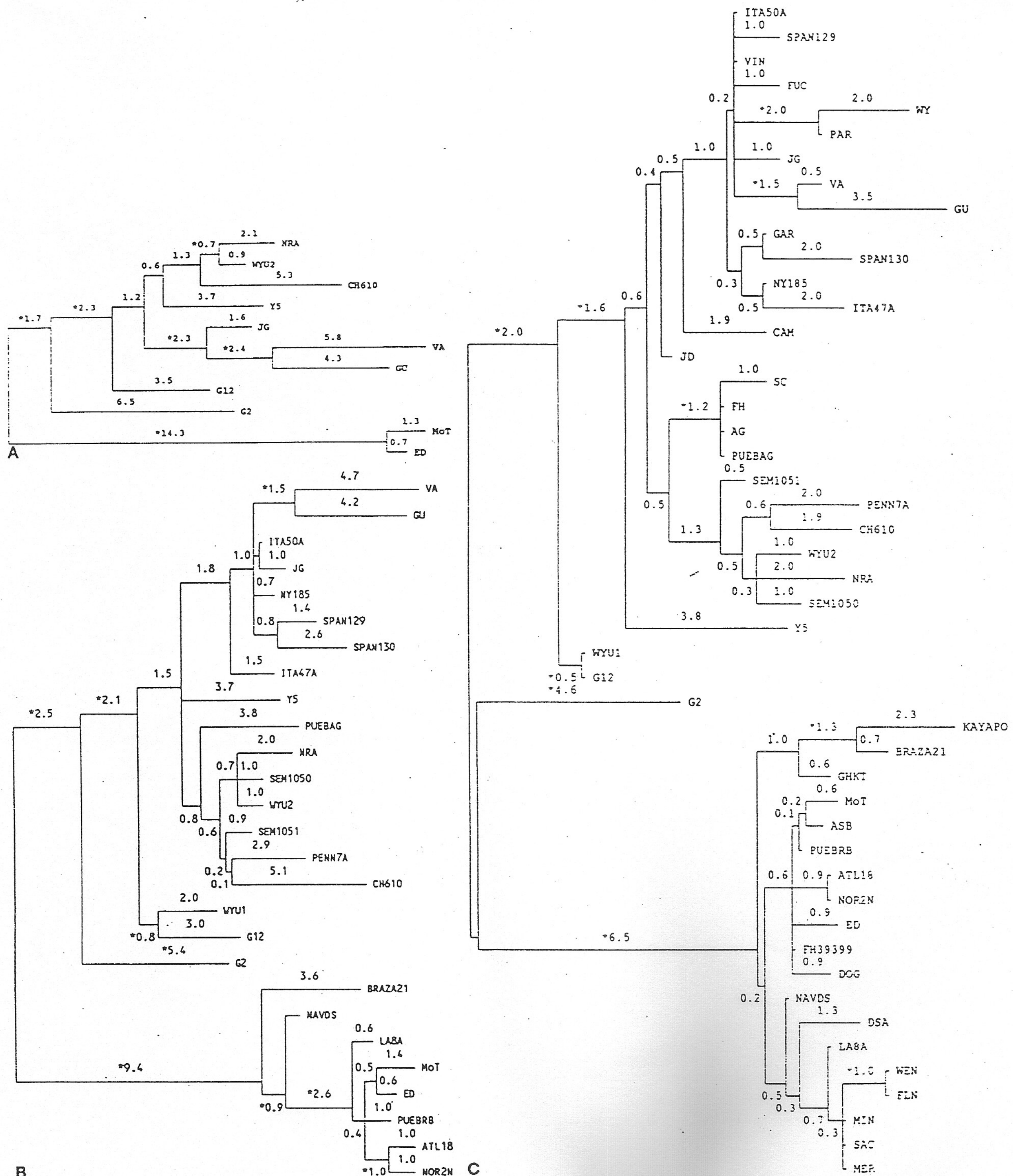

FIG. 3. Cladograms showing the phylogenetic relation of the homologous long terminal repeat (LTR) sequences from the Venezuelan Indian HTLV-II strains G2 and Y5 to other HTLV-IIB (ITA50A; SPAN129; VW; FUC, WY; PAR; JG; VA; GU; SPAN 130; ITA47A; CAM; JD; SC; FH; AG; PUEBAG; SEM1051; PENN7A; CH610; WYU2; NRA; SEM1050; WYU1; G12) and HTLV-IIA (Kayapo; BRAZA21; GHKT; MoT; ASB; PUEBRB; ATL18; NORZN; ED; FH39399; DOG; NAVDS; DSA; LA8A; WEN; FLN; MIN; SAC; and MER) strains. The numbers listed with each branch represent the percentage of divergence of that particular branch. The asterisk denotes branches with a >75% bootstrap value. Sets **A**, **B**, and **C** represent comparisons of LTR sequences between bases 48 to 603, 86 to 603, and 311 to 603, respectively, of the HTLV-II NRA LTR.

those ≤20 years of age, the prevalence was 3 of 10 (30%) ($p = 0.03$, Fisher's exact t-test). The mean age of the 5 seronegative, PCR-positive Indians was 20 years (2, 12, 28, 30, and 38 years), whereas the mean age of the seropositive Indians was 45 years (range, 18–90 years), but the number of seronegative samples is too small to allow for reliable statistical analysis. In those maternal and marital associations that could be analyzed, infection was demonstrated in the offspring of 2 of 10 (20%) infected mothers, whereas 5 of 7 (71%) positive women were married to infected men. Figure 4 illustrates the HTLV-II prevalence in a Yaruro family.

DISCUSSION

Our observations described herein support the original observation that HTLV-IIB infection is endemic among the Yaruro and Guahibo Indians of Venezuela (25,26). As anticipated, and consistent with other reports (12,20–22,35–38), evidence supporting perinatal and sexual transmission was obtained, with the latter mode of dissemination being slightly more common. In this and other published studies conducted on infected families in breast feeding populations, perinatal transmission rates ranged from 10% to 30%, whereas adult, and particularly spousal, infection rates ranged from approximately 40% to 70%. The high prevalence of infection observed in the Indian groups we studied compared with other HTLV-infected populations presumably results from their absolute need for breast feeding, their practice of polygamy, their inbred nature, and the fact that we examined family members of previously identified HTLV-II–positive people. Unlike other HTLV-infected populations, no statistically significant increased prevalence of infection was found in females relative to males. This could result, in part, from the practice of polygamy, which would increase the number of women to whom a male would be exposed over his lifetime. Although the HTLV-IIB strains identified in the Yaruro and Guahibo Indians are unique, no marked structural nor functional differences could be discerned when they were compared with other HTLV-IIB strains. However, complete sequencing will be required to assess these variants fully. Because G-2 is the most divergent HTLV-IIB strain identified to date and because virus has been isolated from this patient, it will be the most likely candidate for further biologic and genetic analyses.

The data further support the hypothesis that HTLV-IIB is endemic throughout Paleo-Amerindian groups and may have been brought by early migrants from Asia or transmitted to them from an animal source after they crossed Beringia 15,000 to 30,000 years ago. Because 1% divergence between the complete genomes of HTLV strains is thought to represent approximately 500 to 1000 years of separation of host populations (12,14,15,20), our genetic data would suggest that the Yaruro and Guahibo Indians have been separated from the Guaymi (Panama), Wayu (Columbia), Toba (Argentina), Mataco-Mataquayan (Argentina and Paraguay), and Seminole (U.S.A.) Indians for 500 to 3000 years and from the Kayapo Indians (Brazil) and other HTLV-IIA infected groups (e.g., the Navajo and Pueblo in North America) by 3500 to >7000 years. Whether these theoretical time frames represent points of genetic divergence or cessation of contacts among Indian groups that could lead to retroviral infections is uncertain.

Our results also continue to highlight the fact that PCR-based formats are more sensitive in diagnosing HTLV infection compared with currently available serologic techniques. They are very similar to previous ob-

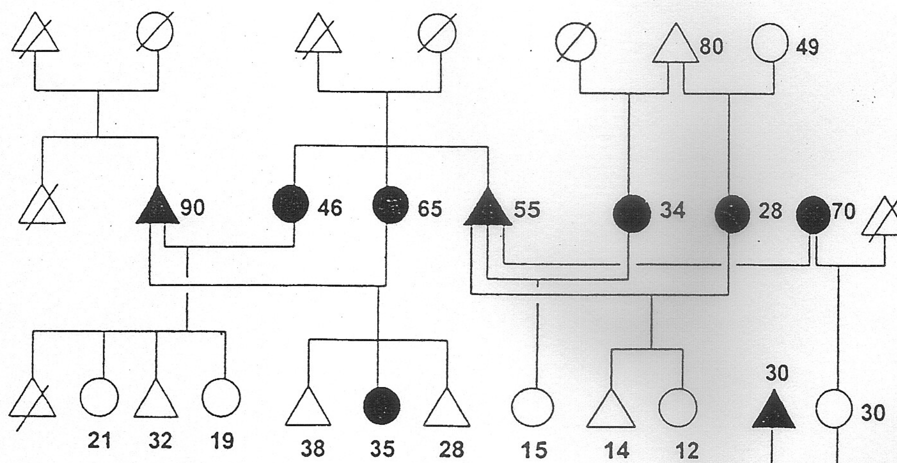

FIG. 4. Pedigree of a Yaruro family. Black circles and black triangles denote infected females and male members, respectively. The ages of the living members are shown beside or below the symbols. Note the practice of polygamy.

servations made by ourselves and others, regardless of whether the target is HTLV-I, HTLV-II, or simian T-cell leukemia/lymphoma virus type I and whether the host is human or nonhuman (39–50). It is conceivable that improved serologic assays, particularly those that also contain HTLV-IIB–specific peptides, might have increased sensitivity for detecting antibodies to HTLV-II in this population (39,40,46).

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