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# Identification and phylogenetic characterization of HTLV-I from a native inhabitant of Easter Island (Rapa Nui)

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**RESUMEN**

Melanesia es una de las tres regiones etnogeográficas en que se dividen las islas del Pacífico siendo esta área endémica para el virus humano linfotrópico de células T tipo I (HTLV-I). Mientras tanto las otras dos regiones como la Polinesia y la Micronesia tienen una muy baja incidencia del virus. En un esfuerzo por interiorizarmos mejor de la prevalencia del virus en estas regiones de Océano Pacífico se hizo un estudio seroepidemiológico en la isla de Pascua, localizada en el extremo este de la Polinesia. En una investigación de 138 sujetos que incluía 108 rapanuis, realizado en la Isla de Pascua, se identificó un caso seropositivo para HTLV-J entre los pascuenses.

Se aisló un nuevo HTLV-I derivado de un portador (E-12) que fue filogenéticamente analizado para entender el origen y la ancestral propagación del HTLV-I a la isla. Este análisis demostró que el virus aislado de E-12 pertenece al sub-grupo A del Grupo Cosmopolita y que difiere claramente del HTLV-I encontrado en la Melanesia que es reconocido como altamente divergente. En el subgrupo A, E-12 es asociado con el HTLV-I sudamericano, que incluye todas aquellas cepas encontradas entre los indígenas de América del Sur. Este resultado sugiere que el virus aislado tiene un origen Sudamericano más que Melanésico.

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## Introduction

Human T-cell leukemia virus type I (HTLV-I) is a human retrovirus, which is considered the etiologic agent of adult T-cell leukemia (ATL) and HTLV-I associated myelopathy/tropical spastic paraparesis (HAM/TSP). This virus is mainly endemic in Africa, Japan, South America, the Caribbean basin, and the Melanesian region (Hinuma et al., 1981; Yanagihara et al., 1990), though sporadic infections of the virus have been found in almost all parts of the world (Tajima et al., 1992). Phylogenetic studies on various HTLV-I isolates have indicated that HTLV-I can be classified into three major groups: the Cosmopolitan (HTLV-Ia) (Gessain et al., 1992), Central African (HTLV-Ib) (Gessain et al., 1992) and Melanesian (HTLV-Ic) groups (Gessain et al., 1993; Nerurkar et al., 1993). Distinct HTLV-I variants of the Central African group recently identified in Central Africa (Chen et al., 1995; Mahieux et al., 1997; Mboudjeka et al., 1997) have been proposed as a fourth group, HTLV-Id, by Mahieux et al. (1997). The Cosmopolitan group is further subdivided into four minor subgroups: the Transcontinental (A), Japanese (B), West African (C), and North African (D) subgroups (Miura et al., 1994; Vandamme et al., 1994; Yamashita et al., 1996). As their names suggest, these phylogenetic groups and subgroups are generally associated with the geographical origins and ethnic backgrounds of the virus carriers. For instance, HTLV-Is found in the Melanesian region are of members of the Melanesian group, while the vast majority of South American HTLV-Is belong to subgroup A of the Cosmopolitan group. This correlation is not unreasonable when we consider that the efficiency of the transmission of HTLV-I is remarkably low and thus horizontal spread through a human population is rare. The low transmission rate is probably the result of a natural transmission mode that requires close and frequent contacts, such as

breast feeding and sexual contact between husband and wife.

The islands of the Pacific Ocean have been intensively surveyed for the presence of HTLV-I because of their geographic proximity to known endemic areas of this disease.

This region is not only adjacent to two endemic foci of HTLV-I, Japan and South America, but it also includes another endemic focus, Melanesia, which is one of the three ethnogeographic regions (Melanesia, Micronesia and Polynesia) of the Pacific Ocean. In contrast, past seroepidemiological surveys have sp far uncovered little evidence of this virus in the other two regions (Tajima et al., 1991; Yanagihara, 1994), except for the case of HTLV-1 infection among some Japanese Americans living in Hawaii (Blattner et al., 1986; Ureta Vidal et al., 1994a). During a recent survey of HTLV-I in Chile, we took advantage of an opportunity to conduct a seroepidemiological survey of the population of Easter Island, which is located on the eastern edge of Polynesia, and thereby to gain new insights on the prevalence of this virus in the Pacific Ocean. During the survey, we identified one HTLV-I seropositive case among the Rapa Nui, the native inhabitants of this island. A new HTLV-I Isolate derived from this carrier (E-12) was phylogenetically analyzed to understand the origin and past dissemination of HTLV-I in the island.

## Materials and Methods

### *Subjects*

In 1996, we performed a seroepidemiological study on HTLV-I infection among 138 inhabitants of Easter Island. Most of the studied inhabitants were Rapa Nui (35 males (mean age=49.7), and 73 females (mean age=45.2)), while the others included 26 people of mixed blood (6 males (mean age=39.8), 20 females (mean age=34.1)), 3 Chilian males (mean age=45.7) and 1 Caucasian female (age=39). To detect and titrate HTLV-I antibodies in plasma, a particle agglutination (PA) test (Fujirebio, Tokyo, Japan) was used. For confirmation, we used an enzyme e immuno assay (EIA) and a Western blot assay (HTLV-I/II BLOT2.4; Diagnostic Biotechnology, Singapore). In the Western blot assay, a serum sample was considered HTLV-I positive when it reacted to Gag (pl9 or p24) and two Envs. One of the envs was the HTLV-I envelope recombinant gp46 peptide (MTA-I) and the other was a common yet specific HTLV-I and HTLV-II epitope recombinant gp21 protein (GD2 1). Human leukocyte antigen (HLA) haplotypes of seropositive subjects were determined as described previously (Blank et al., 1995).

### Polymerase Chain Reaction (PCR)

DNA was extracted by a conventional method using proteinase K from peripheral blood mononuclear cells (PBMCs) which were obtained from whole blood samples by the Ficoll gradient method. Thereafter, DNA was subjected to nested PCR to amplify a part of the long terminal repeats (LTR) region which is approximately 590-bp long and corresponds to positions 99 to 685 in ATK, the prototype Japanese HTLV-I strain (Seiki et al., 1983). The nested PCR conditions and the oligonucleotide primers for amplification were described previously (Yamashita et al., 1995). In addition, we amplified a part of the env gene (522 bp long) which includes the carboxyl terminus of gp46 and almost the entire transmembrane protein gp21, as described previously (Mboudjeka et al 1997). Special care was taken in the PCR experiment to avoid contaminating the amplified products. All the genomic DNAs were manipulated in a room free from the amplified products, and a negative control was used in each PCR experiment.

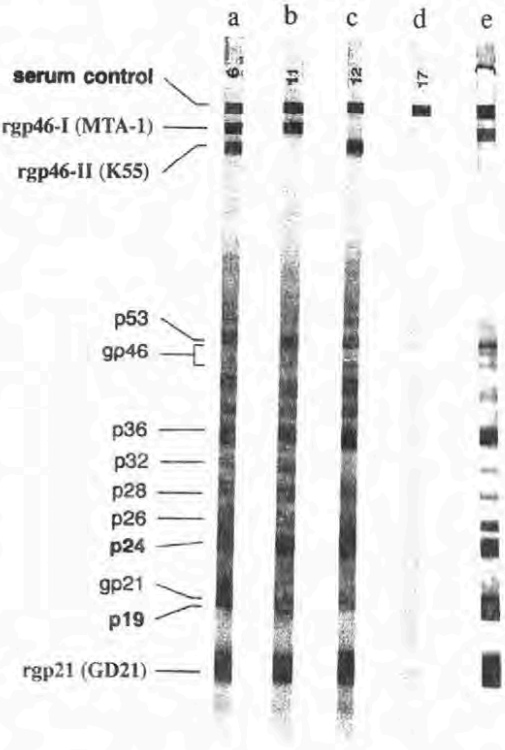
### Subcloning and Sequencing

The amplified fragments of the LTR region were subcloned into the plasmid vector pUC119 using the TA cloning method. Approximately 500-bp-Iong sequences of the LTR region (positions 122 to 628 in ATK) were determined from the cloned PCR products. We sequenced one clone, since nucleotide sequences from different clones of a sample were virtually identical in our previous investigation. The fragment was sequenced in both directions, yielding a 507-bp-Iong nucleotide sequence. A fragment of the partial env gene was directly sequenced after purification of the PCR products with phenol/ chloroform extraction. The nucleotide sequences were determined by using an automated DNA sequencer (Applied Biosystems, Foster City, CA). The new nucleotide sequences in the present study have been deposited in GenBank with the accession number AF013221 and AF132300.

### Phylogenetic Analysis

For construction of phylogenetic tress, each set of

nucleotide sequences newly obtained and previously reported was aligned by using the computer software CLUSTAL W (Thompson et al., 1994) with minor manual modifications. All phylogenetic trees in the present study were constructed by using three methods: the neighborjoining (NJ) method (Saitou et al., 1987), the maximum parsimony (MP) method, and the maximum likelihood (ML) method. We used CLUSTAL W for construction of the NJ trees, and PHYLIP version 3.52 (Felsenstein, 1993), a phylogeny inference package, for construction of the MP trees. In order to know the robustness of the constructed the NJ trees, bootstrapping (Felsenstein, 1985) was done to generate 100 resamplings of the original sequence alignments and pairwise genetic distances were estimated on each resampling by Kimura's two-parameter method (Kimura, 1980). For the MP trees, one hundred resamplings of the original alignment were generated using the SEQBOOT program and then the most parsimonious trees were generated from bootstrapped sequence data using the DNAPARS program. The majority-rule consensus MP tree was generated using the CONSENSE program. The ML trees were generated with the DNAML program (global rearrangements, randomized input order, and outgroup rooting options «on»). The empirical transition/transversion bias was 4.5 for the partial LTR (507bp-long) analysis and 3.2 for the gp2l env (522bp-long) analysis. Since the statistical evaluation of the branch length and branching nodes is a built-in feature of the DNAML program, bootstrapping was not done in the ML method. The trees were visualized with TREEVIEW (Page, 19W). In this report, the phylogenetic trees constructed by the NJ method are shown because the trees constructed by tbe MP and ML methods were virtually identical to those constructed by the NJ method.




a = HTLV-I/II dual infection serum
b = Strong reactive HTLV-I control
c = Strong reactive HTLV-II control
d = Non-reactive control
e = E-12 (PA titer = x256)

Figure 1. Western blot profiles of antibodies from the plasma sample of E-12. rgp46-I (MTA-I) is a unique HTLV-I envelope recombinant gp46 protein, while rgp2 1 (GD2l) is a common yet specific HTLV-I and II epitope recombinant envelope gp21 protein.

## Results

Of the 138 inhabitants of Easter Island, one 58-year-old Rapa Nui female (E-12) was found to be PA and EIA positive. The titer of HTLV-I antibodies in this subject was 1/256 in the PA test. Seropositivity of the subject was confirmed by a Western blot, showing specific HTLV-I antibodies with p24, pl9, rgp46-I and GD2I seroreactivity (Figure 1). The other tested subjects were seronegative by the PA test. The seropositive subject had no history of blood transfusion and denied intravenous drug use. We had no information about history of homosexual or nonmonogamous heterosexual activity in this subject. The sister of E-12 (34 years old) was seronegative by the PA test, while the subject's husband and parents were not studied. HLA analysis of E-12 indicated that the inferred HLA haplotypes are A2 B55/B56/ DR12/B39 DR4, suggesting that this patient is of mixed blood with Amerindian and Maori ancestry (Imanishi et al., 1992). Maoris are the indigenous inhabitants of New Zealand. These observations indicate that HTLV-I does exist but is rare in Easter Island.

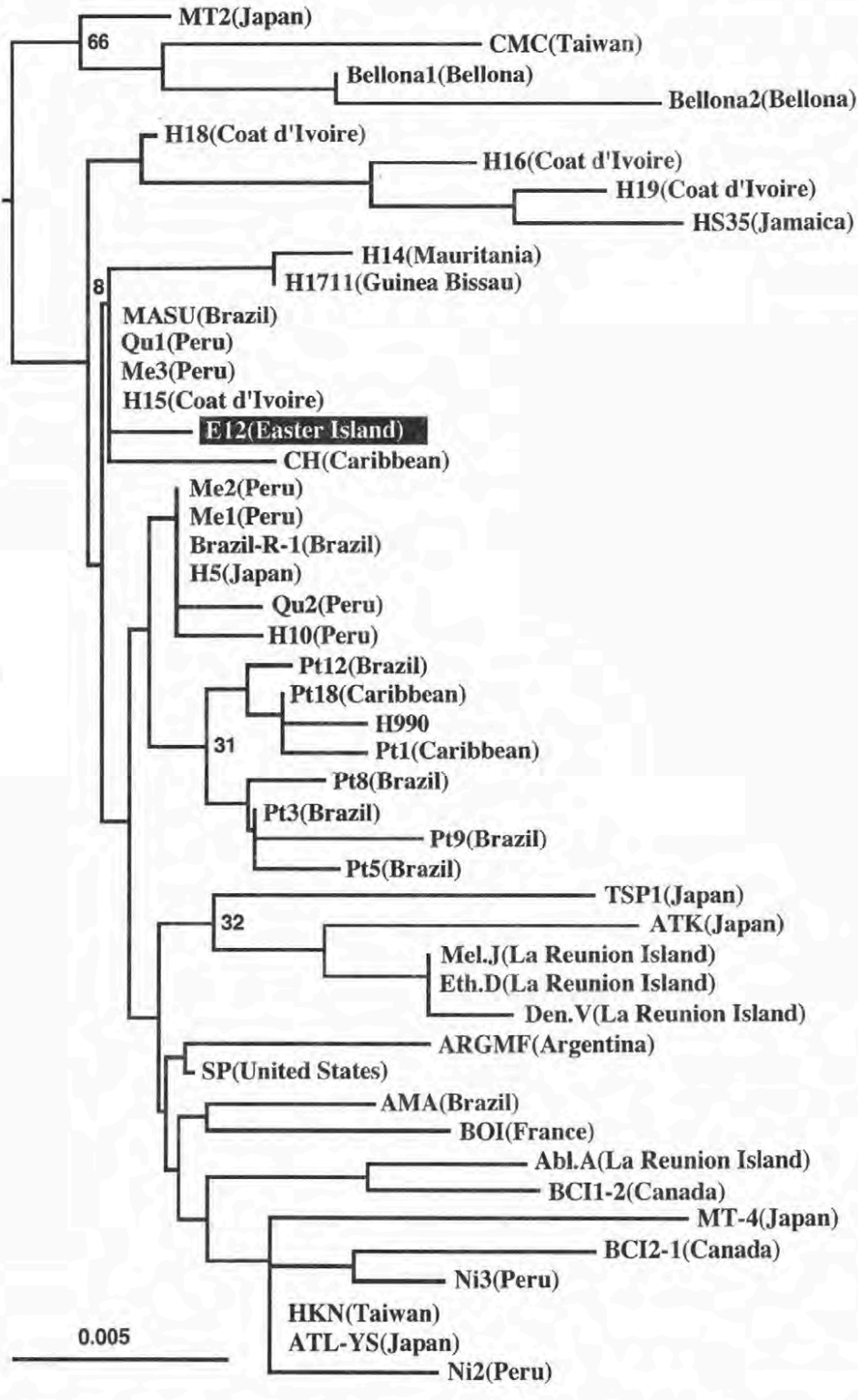



Figure 4. Phylogenetic tree of HTLV-Is based on the partial *env* gene (522-bp-long). The tree was constructed by using the NJ method. MelS was used as the outgroup. For other details, see the legend of figure 2.

In order to know the evolutionary relationships of this new HTLV-I isolate with other HTLV-Is of various geographical origins, we phylogenetically characterized the new isolate. A phylogenetic tree constructed with the NJ method and based on the partial LTR region (507-bp Long) is shown in Figure 2. In the figure, the new HTLV-I isolate (E-12) is clearly a member of the Cosmopolitan group and furthermore, it belongs to the Transcontinental (A) subgroup. Phylogenetic trees constructed with the MP and ML methods gave essentially the same results. Despite the subject's geographical location (Easter Island) and ethnic origin, the new isolate did not show strong similarity to the HTLV-Is of the Melanesian region. In fact, the LTR sequence of this isolate differed from MELS (an isolate of the Melanesian group) by 8.3%, whereas only 2.6% difference was observed between E- 12 and ATK (the prototypic strain of HTLV-I, which belongs to the Cosmopolitan group). This was also confirmed by the restriction fragment length polymorphism (RFLP) profile according to the classification system proposed by Ureta Vidal et al. (1994b). The RFLP pattern of E-12 indicated that the LTR of E-12 had the Mae II, Nde I and Sac I sites, but not the Ava I and Mae III sites, which was consistent with the RFLP pattern of subgroup A and differed from that of the Melanesian group. These findings were further confirmed by comparison of the gp21 env gene nucleotide sequence between E-12 and Melanesian HTLV-I (data not shown). The partial env of E-12 belonged to the Cosmopolitan group based on an amino acid substitution that is specific to this group: the env has a V at position 230 in ATK, while the other groups have M or I. These results indicate that E-12 belongs to subgroup A of the Cosmopolitan group but markedly differs from the Melanesian group of HTLV-I (HTLV-Ic).

In a tree constructed with the NJ method that includes almost all the HTLV-Is of the subgroup A (Fig. 3), the new isolate (E-12) made a cluster with HTLV-Is of South America. Although the bootstrap value supporting this cluster was not very high, we observed two common nucleotide variations among all the HTLV-Is in this cluster. Namely, the new isolate as well as those belonging to this cluster have C at position 479 and G at position 528 (the positions correspond to those of ATK), whereas all the other HTLV-Is of the subgroup A have T at position 479 and A at position 528.It is interesting that most HTLV-Is of Amerindians from Colombia have been shown to belong to the same cluster that the new isolate is in (Miura et al., 1994). Phylogenetic trees based on the MP and ML methods reproduced this cluster, which support the close relatedness between E-12 and South American HTLV-Is.

Cosmopolitan HTLV-Is have been identified in Bellona Island, a Polynesian outlier within the Solomon archipelago (Yanagihara et al., 1991). These HTLV-Is were genetically analyzed based on the partial env gene (Gessain et al., 1991; Nerurkar et al., 1993). To compare the new HTLV-I (E-12) with these isolates, we sequenced a part of its env gene (522bp long) (Fig. 4). The NJ tree based on the partial env gene showed that E- 12 did not group with HTLV-Is from Bellona BEL1 and BEL2), which showed more similarity to Far East Asian isolates (MT2 and CMC). The trees based on the MP and ML methods also failed to disclose a relatedness between the HTLV-Is of Bellona and Easter islands. Instead, the HTLV-Is from Bellona Island have two common nucleotide variations with two Far East Asian HTLV-Is (MT2 and CMC) (G at position 6168 and T at position 6219, whereas all the other HTLV-Is of the Cosmopolitan group including E-12 have A at position 6168 and C at position 6219). Thus, these results do not reveal any strong association among Polynesian HTLV-Is.

## Discussion

What is the source of the new HTLV-I isolate found in the Rapa Nui woman in this study? It is commonly believed that the Rapa Nui descended from Polynesians who came to Easter Island at about 400 A.D. However, there has been extensive contact between the Rapa Nui and South Americans. For example, Peruvian slavers carried away almost all the island's males in the middle of the 19th century.

The subsequent repatriation of some males introduced smallpox to Easter island, which devastated the remaining native inhabitants.In addition, annexation of Easter Island by Chile in 1888 brought massive human migrations from South America. Thus, it is uncertain whether the present native inhabitants are really pureblooded natives or not. Given the extensive contacts between Easter Islanders and South Americans during the past few centuries, and the generally accepted idea that the virus was present in South America, at least by the 19th century (Gessain et al., 1996; Yamashita et al., 1996), it is very likely that the new HTLV-I isolate originated in South America. This is also supported by the subject's HLA haplotypes, which

are frequently found in Amerindians. This may mean that the virus was from an Amerindian, some of whom are known to be infected with HTLV-Is that are closely related to the new isolate.

In contrast, the possibility for direct dissemination of HTLV-I from other parts of the Pacific islands to Easter Island must be quite low. The marked difference between the new HTLV-I from Easter Island and the HTLV-Is of the Melanesian region argues against the introduction of the new isolate from the Melanesian region. In addition, although Polynesians are considered to be the first settlers of Easter Island, a Polynesian origin of the new isolate also seems unlikely, as the two HTLV-Is of the Cosmopolitan group from Bellona Island, based on the gp21 env gene sequence, were not closely related to the new isolate. Our recent study, in which BEL1 was analyzed based on the LTR region, supported the env-based phylogenetic analysis, showing that E-12 make a cluster with BEL1 (data not shown). Nonetheless, the present results do not completely exclude the possibility that the new isolate is a relic of a past endemic of the virus in Polynesia, since there is still little data on the prevalence of HTLV-I in Polynesia. On the other hand, sporadic infections recently identified in residents of the Marshall Islands and Nauru (Miller et al., 1998; Nicholson et al., 1992), both of which are situated in the Micronesian region, leave open the possibility of some transmission of HTLV-I from Micronesia to Easter Island. In summary, our findings strongly suggest that the new isolate of HTLV-I in Easter Island originated in South America. However, it is evident that more data is needed to understand the past dissemination of this virus in the Pacific Ocean.

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