**Macaca fascicularis** papillomavirus type 1: a non-human primate betapapillomavirus causing rapidly progressive hand and foot papillomatosis

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Papillomaviruses (PVs) are a group of small, non-enveloped DNA viruses that cause mucosal or cutaneous neoplasia in a variety of animals. Whilst most papillomas will regress spontaneously, some may persist or undergo malignant transformation. In this study, aggressive, persistent and extensive warts were observed on the hands and feet of a cynomolgus macaque (**Macaca fascicularis**). The presence of PV in the wart biopsies was identified by immunohistochemistry and PCR amplification of PV DNA. The genomic DNA of this PV was cloned and sequenced, and the PV was designated **M. fascicularis** papillomavirus type 1 (MfPV-1). Its genome was 7588 bp in length and the organization of its putative open reading frames (E1, E2, E6, E7, L1, L2 and E4) was similar to that of other PVs. MfPV-1 had a short non-coding region (NCR) of 412 bp. Molecular analysis of MfPV-1 genomic DNA classified it into the genus **Betapapillomavirus**, to which all epidermodysplasia verruciformis (EV)-type PVs belong. Diseases caused by PVs of the genus **Betapapillomavirus** are usually associated with natural or iatrogenic immunosuppression. The genomic characterization performed in this study showed that MfPV-1 clustered within the genus **Betapapillomavirus** and also contained EV-type-specific motifs in its NCR. Further characterization of this virus and its host interactions may allow us to develop a non-human primate model for human betapapillomaviruses, a genus populated by human PV types causing EV.

**INTRODUCTION**

Papillomaviruses (PVs) infect cutaneous and mucosal epithelial cells and cause both benign and malignant hyperproliferative lesions (Chang et al., 1990; Jenson et al., 2001; Howley & Lowy, 2007). PVs are ubiquitous and have been identified as infectious agents in birds and mammals (Sundberg & Reichmann, 1993). Of the nearly 100 types of human PV (HPV) sequenced so far (de Villiers et al., 2004; Howley & Lowy, 2007), approximately 40 % are mucosotropic, with the rest infecting the skin. PVs are a group of small, naked, icosahedral viruses with a double-stranded DNA genome of 7–8 kb. Despite their highly conserved genomic organization, each PV type is species- and tissue-specific. Whilst initial PV infection occurs at the basal cell layer of the epithelium, the maturation of new viruses occurs at the surface of the epithelium, where PV capsid proteins are abundantly expressed. This occurs in koilocytic cells, which display the cytopathic effects of PV infection, express large amounts of capsid proteins and are only observed on the surface of fully developed warts (Howley & Lowy, 2007). Because PVs cannot be replicated in conventional cell culture and infectious transmission of PVs between species has not been reported, an ideal animal model for HPVs of the genus **Betapapillomavirus** has yet to be developed. HPVs may be causally linked to as many as 99.7 % of cervical cancers and are also involved in head and neck cancers (Psyrri & DiMaio, 2008) and lung cancers (Hajdu & Ali, 2008).

The family Papillomaviridae consists of at least 18 separate genera, three of which (**Alpha-**, **Beta-** and **Gamma-papillomavirus**) contain 80 % of all known PVs and are entirely composed of primate PVs. Alphapapillomaviruses (α-PVs) are found in mucosal and cutaneous lesions in humans and primates, whereas betapapillomaviruses (β-PVs) and
gammapapillomaviruses (γ-PVs) have been isolated exclusively from cutaneous lesions. β-PVs are also referred to as ‘EV-type HPVs’ due to their close association with epidermodysplasia verruciformis (EV) in humans (de Villiers et al., 2004). The remaining genera contain mostly animal PVs. The involvement of PVs in EV was first demonstrated in 1972 (Jablonska et al., 1972) and was confirmed experimentally 7 years later (Orth et al., 1979). EV-type HPVs are usually asymptomatic in the normal population, but can cause non-melanoma skin cancer among genetically or iatrogenically immunocompromised patients (Harwood et al., 2000; Pfister et al., 2003; Orth, 2006). Although not a common disease, EV is considered serious because it causes persistent, refractory and disseminated skin lesions resembling flat warts or macules of various colours that are resistant to all conventional treatments (Orth, 2006). Following exposure to sunlight, these lesions may undergo malignant transformation (Gül et al., 2007). To date, however, the viral and cellular molecular mechanisms leading to the development of skin malignancies in EV patients are not completely understood.

In this study, we characterized the genomic DNA of Macaca fascicularis papillomavirus type 1 (MfPV-1), isolated from a cynomolgus macaque. Macaques are the most widely distributed genus of non-human primates and have been commonly used in medical research, most recently in the study of AIDS (Maggiorella et al., 2007). The availability of cynomolgus macaques in animal-research facilities and the characterization of MfPV-1 as a member of the β-PVs may allow us to understand the biology of human β-PVs, including EV-type HPVs, using MfPV-1 as a candidate animal model.

METHODS

Wart tissue samples. Cutaneous papilloma biopsies were collected from an 8-year-old, male cynomolgus macaque, which presented with thousands of benign papillomas of different sizes on its extremities. This animal had been in the USA for approximately 5 years. It was transferred to the animal facility of the University of Miami, FL, USA, and quarantined according to standard procedures. Following this quarantine period, the animal developed plantar and palmar warts, prompting its subsequent removal from the colony prior to experimental use. Punch biopsies (5 mm) of the warts were taken from a foot. Biopsies were snap-frozen and shipped to the University of Louisville, KY, USA, on dry ice and stored at −70 °C until further use.

Indirect immunofluorescence assay. The presence of PV antigen in cells was examined by an indirect immunofluorescence assay. Frozen tissue sections (8 μm) were cut by using a cryostat, loaded onto glass slides and fixed in cold acetone for 5 min. After rehydration in PBS, tissue sections were incubated with murine monoclonal antibody (mAb) AU-1 (Covance) at a 1 : 100 dilution in PBS for 1 h at room temperature. The mAb AU-1 was generated against denatured bovine papillomavirus type 1 (BPV-1) virion and recognizes a cross-reactive sequential epitope (TYRR) existing on the major capsid proteins of many PVs (Lim et al., 1990). After three washing steps with PBS, fluorescein isothiocyanate (FITC)-labelled goat anti-mouse IgG (Sigma) at a 1 : 100 dilution in PBS was added for 1 h. Slides were observed under a fluorescence microscope (Olympus).

Identification of small, circular viral DNA, its cloning and DNA sequencing. Sections (approx. 2 mm thick) from the centre of a wart biopsy were minced finely with a scalpel. Complete DNA was purified from the biopsy by using a DNA isolation kit (DNeasy Blood and Tissue kit; Qiagen). A rolling-circle amplification (RCA) protocol was used to determine the presence of small, circular PV DNA. RCA was performed according to the manufacturer’s instructions (TempliPhi 100 Amplification kit; Amersham Biosciences) with minor modifications (Rector et al., 2004). Briefly, approximately 1 μg DNA extract was added to 5 μl sample buffer containing random hexamer primers, denatured at 95 °C for 3 min and incubated at room temperature for 5 min. TempliPhi reaction buffer (5 μl), 0.2 μl TempliPhi enzyme mix and 450 μM additional dNTPs were added to the denatured DNA. The mixture was incubated overnight at 30 °C, followed by inactivation for 10 min at 65 °C. A 0.2 μl aliquot of amplified DNA was incubated with 10 U of each restriction enzyme (SacI, KpnI, Xhol, SadI, XbaI, BglII and BgIII) and loaded on a 0.8 % agarose gel. The presence of one or multiple bands with sizes adding up to full-length PV DNA (approx. 8 kb) was examined.

To clone full-length MfPV-1 DNA, 10 μl of the RCA product was digested with the unique restriction enzyme SadI. The digestion product was run on a 0.8 % agarose gel and DNA fragments were extracted by using a QIAquick Gel Extraction kit (Qiagen). Purified DNA was cloned into the SadI site of the pUC19 vector digested with SadI and gel-purified. To confirm the presence of PV DNA in these clones, the clone was sequenced with an M13 primer set.

To facilitate obtaining the full-length MfPV-1 genomic DNA sequence, an EZ::TN <KAN-2> Insertion kit (Epicentre Biotechnologies) was employed. Briefly, 0.2 μg MfPV-1 clone in pUC19 was mixed with 1 μl EZ::TN reaction buffer, an equimolar amount of the transposons and 1 μl Tn5 transposase. The mixture was incubated at 37 °C for 2 h, after which the reaction was stopped by adding 1 μl stop solution and heating at 65 °C for 10 min. The mixture was transferred to recA− E. coli and plated on kanamycin-containing plates. DNA obtained from colonies was sent either to the Nucleic Acids Core Facility at the University of Louisville or to MWG Biotech for sequencing with the supplied primers. For assembly and confirmation of the full-length PV genomic sequence, the sequencing data were submitted to the SeqMan II program (DNASTAR) and aligned with other known PV genomic DNA sequences. Parts of the genome that were sequenced on one genomic strand only were confirmed by primer walking.

MfPV-1 genome sequence analysis. The open reading frames (ORFs) of the MfPV-1 genome were analysed using the EditSeq program (DNASTAR). The molecular masses of the encoded putative proteins were calculated using the Mapdraw program (DNASTAR). Amino acid sequences of these putative proteins were then compared with those of other PVs to determine any possible binding domains reported previously for PVs. To obtain a detailed map of transcription factor binding sites on the MfPV-1 genome, the MfPV-1 genomic DNA sequence was submitted to the Transcription Element Searching System (TESS; http://www.cbil.upenn.edu/tess) (Schug & Overton, 1997).

Sequence similarity and phylogenetic analysis of MfPV-1. Phylogenetic analysis included the genomes of MfPV-1, the representative HPV type species (de Villiers et al., 2004) and all animal PVs for which the whole genome was available. The E1, E2, L1 and L2 nucleotide and amino acid sequences for these PVs were downloaded from GenBank. These sequences were then aligned by using standard settings in MUSCLE (a multiple sequence alignment method with reduced time and space complexity; Edgar, 2004).
visual inspection of the separate alignments, the concatenated alignment was opened in PAUP* (Swofford, 2002; Wilgenbusch & Swofford, 2003) and used to construct a neighbour-joining tree. Bootstrap support values were calculated for 1000 replicates.

RESULTS

Clinical presentation of the index case

The animal from which this PV was isolated exhibited no signs of illness during its quarantine period. The first warts appeared on the animal’s hand after quarantine, spreading extensively across its palms and soles (Fig. 1). The warts on this animal did not show any sign of regression. None of the other animals in the same housing facility ever showed any similar lesions. Immunohistochemistry with mAb AU-1, which is reactive with a cross-reactive, genus-specific, sequential epitope of PV, showed that the nucleus of surface epithelial cells in the lesion expressed large amounts of PV capsid proteins (Fig. 2).

Identification of the viral genome

RCA preferentially amplifies small, circular DNA such as PV DNA. As shown in Fig. 3, DNA extracted from the wart biopsy of this infected cynomolgus macaque contained DNA that could be replicated by using the RCA method. After digesting the high-molecular-mass RCA product with Xhol, BglII or BglII, two bands were identified that were approximately 7.5 kb in combined length. Both Xhol and SacI produced distinctive single bands with a molecular size of approximately 7.5 kb each, which identified them as unique sites on the genomic DNA of this monkey PV. The RCA DNA product was then cloned into the SacI site of the pUC19 vector. According to the accepted classification of PV, a newly isolated PV can be categorized as a new PV type if its genomic DNA is cloned and fully sequenced and its L1 DNA sequence differs by >10% from the closest known PV type (de Villiers et al., 2004). BLAST analysis of the primary sequence data found no PV DNA with sequence identity of >75% to this newly isolated PV DNA, confirming it as a novel PV. The complete sequence, which was obtained by using an EZ::TN <KAN-2>
Genomic organization of MfPV-1 and putative binding-site analysis

Similar to all other known PVs, MfPV-1 has all of its ORFs on one DNA strand and the genome can be divided into three regions: early (E), late (L) and non-coding (NCR). The E and L regions cover 52.2 and 41.1 % of the genome, respectively. The E region contains four ORFs encoding the E1, E2, E6 and E7 proteins, whilst the L region consists of two ORFs encoding the L1 and L2 structural proteins. The genomic organization of MfPV-1 is depicted in Fig. 4. The first nucleotide of the E6 ORF was assigned position 1, with the translation start codon for E6 at position 7. Amino acid alignments revealed an E4-like sequence within E2, but it lacked a start codon. No E5 sequence could be identified. The NCR located between the L1 and E6 genes was 412 bp. The nucleotide position, size and predicted molecular mass of each ORF as well as the location and size of the NCR are detailed in Table 1.

PVs use the host’s cellular machinery to replicate and transcribe their genome and to translate their genes, as do most viruses. The NCR, which is located upstream of the E genes but downstream of the L genes, contains most, if not all, of the regulatory elements, such as the major viral promoter and several putative recognition sites for cellular and viral transcriptional factors (Zheng & Baker, 2006; Howley & Lowy, 2007). According to tESS (Schug, 2008) and a comparison of all well-studied PV genomes, MfPV-1 may contain eight PV E2 protein-binding sites (E2BSs): four typical palindromic E2BSs, 1–4 (ACCN6GGT), the slightly modified E2BS 5 (AACN6GTT) in the NCR, two additional E2BSs on the L2 gene (6 and 7) and E2BS 8 on the L1. We also located one putative E1-recognition site (AATGGTTGTGGCCAACACCCATT) at position 7469, which is in the middle of two E2BSs as found in other PVs (Berkhout et al., 2000; Van Doorslaer et al., 2007). We identified putative polyadenylation sites and a 19 bp AT stretch at the 3’ end (nt 7545) of the NCR. The AT stretch is conserved among EV-type PVs, but was rather short in MfPV-1 compared with those of HPV-20 and -47 (57 and 31 bp AT stretches, respectively). It has been suggested that this AT stretch could be the TATA box as the major promoter for the early and late viral proteins (Fuchs & Pfister, 1997).

We identified numerous putative binding sites for transcription factors. The NCR carried putative binding sites for AP1, NF1, GATA-1 and -3 and E2F. The MfPV-1 NCR has a short (412 bp) NCR, characteristic of EV-type PVs in the genus Betapapillomavirus (HPV-5 and -47 have NCRs of 478 and 486 bp, respectively; Fuchs & Pfister, 1997). The reasons why the NCRs of β-PVs are shorter than those of the other PVs are not known. Like the other EV-type PVs, MfPV-1 had the above-mentioned binding sites spread into ORFs adjacent to the NCR (Fig. 5). It has been hypothesized that this arrangement allows the members of the genus Betapapillomavirus to compensate for their short NCRs (Fuchs & Pfister, 1997).

The E6 protein of MfPV-1 possessed two zinc-binding domains (CX3C-CX3C-C) and the E7 protein had one zinc-binding domain and a putative pRb binding motif (LXCXE). In addition, six putative p300-binding sites and three nuclear factor-κB (NF-κB)-binding sites on the E6 and E7 sequences were found (Fig. 5). E6 and E7, which bind to p53 and pRb, respectively, are the major PV oncoproteins (Howley & Lowy, 2007). The E6 ORF also contained four NF1-, one YY1-, two SP1-, one GATA-1-, two Oct-1- and one AP1-binding sites. The E7 ORF had seven putative SP1-binding sites in addition to four GATA-1-, one AP1-, one GATA-3- and one NF1-binding sites. The E4 sequence located within the E2 had a typically high G + C content (53.6 mol%). The putative E4 protein was proline-rich (25.7 %), similar to that of other PVs. The MfPV-1 E1 gene encoded a 603 aa protein. The E2 protein had an ATP-binding site (GGPNTGKS), suggesting that it may maintain its ATP-dependent helicase function (Titolo et al., 1999). MfPV-1 E2 contained the
conserved DNA-binding α-helix (GDANTLKCFRNR) (McBride et al., 1989).

The L region of MfPV-1 contained the ORFs for the L2 (nt 4063–5634) and L1 (nt 5644–7182) proteins, with predicted molecular masses of 56.8 kDa (523 aa) and 58 kDa (512 aa), respectively. MfPV-1 L1 had a larger predicted molecular mass than that of the other PVs, which have molecular masses between 55 and 57 kDa. Like all other PV L1 and L2 proteins, MfPV-1 L1 and L2 had putative nuclear-localization signals at their C termini (RRKRK and KRKRK, respectively). Interestingly, MfPV-1 maintained an epitope (TYRY; Lim et al., 1990) recognized by mAb AU-1, which was made against the denatured BPV-1 virion (Cowsert et al., 1987).

### Table 1. Positions of the ORFs and NCRs of MfPV-1 and the predicted molecular masses of the translated proteins

<table>
<thead>
<tr>
<th>ORF</th>
<th>Start</th>
<th>Stop</th>
<th>Length</th>
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<td></td>
<td>nt</td>
<td>aa</td>
<td></td>
<td></td>
</tr>
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<td>E6</td>
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<td>423</td>
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<td>138</td>
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<td>603</td>
</tr>
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<td>3970</td>
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<td>503</td>
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<td>3725</td>
<td>756</td>
<td>–</td>
</tr>
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<td>L2</td>
<td>4063</td>
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<td>523</td>
</tr>
<tr>
<td>L1</td>
<td>5644</td>
<td>7182</td>
<td>1539</td>
<td>512</td>
</tr>
<tr>
<td>NCR</td>
<td>7183</td>
<td>6</td>
<td>412</td>
<td>–</td>
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</table>

*E4 does not have an identifiable start codon in the ORF.

NA, Not applicable.

Phylogenetic analysis of MfPV-1 and sequence similarity

We constructed a neighbour-joining phylogenetic tree based on a concatenated alignment of the nucleotide and amino acid sequences of E1, E2, L2 and L1. In this tree, MfPV-1 clustered with HPV-5 and -47 as a member of the genus Betapapillomavirus (Fig. 6). According to pairwise sequence analysis of MfPV-1 with members of the genus Betapapillomavirus, the highest similarities were found in the L1 and E1 ORFs. The genomic DNA of MfPV-1 shared <75% sequence similarity with any of the PVs that have been completely sequenced and characterized. The MfPV-1 L1 gene shared 64–73% similarity with that of the other members of the genus Betapapillomavirus, whilst sharing <60% similarity with any other PV L1 genes. According to the PV classification system, this places MfPV-1 in the genus Betapapillomavirus (de Villiers et al., 2004).

Finally, to ascertain that MfPV-1 was a novel virus, we also performed pairwise sequence alignments between MfPV-1 and all previously reported monkey PV sequence data (Table 2). This analysis confirmed that MfPV-1 is a novel PV.

### DISCUSSION

We isolated a novel PV from a macaque housed in an experimental animal facility. Because non-human primates have been employed as model organisms in biomedical research (Maggiorella et al., 2007), it is pivotal to keep them in a disease-free state. Severe cutaneous papillomas were seen on the hands and feet of a cynomolgus macaque during routine clinical examination. This non-human primate was one of several acquired for transplantation experiments at an academic research institution. Prior to experimentation, the

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**Fig. 5.** Putative binding sites for transcription and oncogenicity. The locations of binding sites recognized by NF1 ( ), AP1 (△), Oct1 ( ), YY1 ( ), GATA-1 ( ), GATA-3 ( ) and Sp1 ( ) are indicated on the DNA line. The putative binding sites of E1, E2, NF-κB and p300 are also indicated on the DNA sequence. Six out of eight potential E2BSs are marked as P1–P6, which are spread from the 3’ end of the L1 ORF to the NCR. The locations of the polyadenylation signal and promoter are indicated as (A) and AT(ATA)8A on the NCR and a TATA box-like sequence was found on the E7 ORF (not shown). As indicated, the E6 and E7 oncoproteins of MfPV-1 have two and one zinc-binding domains (CX2C-X29-CX2C) ( ● ● ), respectively. A pRb-binding domain (★) was located on the E7 protein.
animal presented with lesions suggestive of an infection, probably PV. Specimens were collected from the affected lesions for isolation of the putative PV DNA.

In humans, warts on the feet and hands are usually associated with HPV-1 and -2. These infections usually occur in pre-teenagers and teenagers, although some infections can last into adulthood. So-called butcher’s warts, which present among meat-handlers with similar clinical features to MfPV-1, are usually caused by HPV-7. HPV-4, although rare, causes mosaic foot papillomas in humans. However, phylogenetic analyses identified MfPV-1 as a member of the genus *Betapapillomavirus* (Fig. 6). MfPV-1 is the first non-human primate PV belonging to the β-PVs for which the complete genome sequence has been characterized. β-PVs in humans are usually associated with EV and have become important viruses to study, due to the particularity of their pathobiology. EV is a rare autosomal-recessive genodermatosis, possibly due to mutations of EVER1 or EVER2 (Ramoz et al., 2002) and is caused by persistent β-HPV infection. These EV-type HPVs have been found in healthy individuals; however, in patients with genetically impaired immunity or patients with iatrogenically induced immunosuppression, they can cause lifelong eruptions of pityriasis versicolor-like macules and flat wart-like papules, leading to the development of non-melanoma skin cancer.

**Fig. 6.** Neighbour-joining phylogenetic tree based on a concatenated E1/E2/L2/L1 nucleotide and amino acid sequence alignment of MfPV-1 and 73 other vertebrate PVs. The PV genera are indicated with their Greek names according to de Villiers et al. (2004). The numbers at the internal nodes represent the bootstrap probabilities (%) as determined for 1000 iterations by the neighbour-joining method.
Recently, a new papillomavirus (canine PV3; CPV-3) was isolated from a malignant canine EV, which presented as pigmented plaques. The genomic DNA of CPV-3 does not share much similarity with members of the genus Betapapillomavirus and was classified into a novel genus (Tobler et al., 2006). Although we do not know whether MfPV-1 causes cancer (the index animal was euthanized shortly after the MfPV-1 strain was identified, as the unusually extensive warts on its palms and soles were considered to be potentially contagious to other animals), the phylogenetic position of this virus, as well as some shared genomic traits that are characteristic of EV-type PVs (AT stretch, short NCR and multiple E2BSs), suggest that MfPV-1 may allow us to study the pathology of EV-PV types in vivo. A recent report on a transmission model for genital PVs in macaques (Wood et al., 2007) indicated the possibility of developing controlled infectivity studies in these animals. One caveat with MfPV-1 and the study of EV-related disease is the observation that not all subjects appear to be equally susceptible to infection. This macaque may have been highly contagious at the time of sample harvest, as indicated by the immunohistochemistry of the affected tissue with mAb AU-1, which detects the L1 major capsid protein of PVs. It is likely that a genetic or immunological defect lies at the basis of this observation. All clinical laboratory test results were normal. Otherwise, we were unable to assess the immunological state of the index case. Only immunocompromised humans develop EV-like manifestations, adding validity to the use of MfPV-1 as a model for understanding EV-type HPVs and their pathobiology.

### Table 2. Comparison of L1 sequences between MfPV-1 and other PVs

The L1 sequences of four non-human primate PVs, three of 25 representative EV-type HPVs, two HPVs related to butcher’s warts and three of 62 partial L1 sequences (under 450 bp in size) of non-human primate PVs collected from GenBank were compared with MfPV-1.

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<th>Host species</th>
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<th>Similarity* nucleotide</th>
<th>Similarity* amino acid</th>
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<td>Complete genome or L1 sequences reported</td>
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</tr>
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*Similarities were evaluated by comparing L1 DNA and protein sequences using the MegAlign program (DNASTAR).

### REFERENCES


