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## An integrated approach to canine oral papillomatosis: histopathology, molecular detection, and b-cell epitope mapping of CPV1 L1 gene

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### ABSTRACT

Canine Oral Papillomatosis, caused by Canine Papillomavirus (CPV), is a contagious disease characterized by the development of benign neoplasms in the oral cavity. Two clinical cases presenting with "cauliflower-like" oral masses, halitosis, and dysphagia were evaluated for a multi-dimensional characterization of L1 gene of CPV. Histopathology confirmed benign neoplastic proliferation with classic exophytic papillary projections and marked acanthosis, supported by a central fibrovascular core. For molecular typing, an optimized DNA extraction protocol involving a 10-minute thermal pretreatment of keratinized tissue was employed. The L1 major capsid gene was amplified via PCR (265 bp), sequenced, and analysed. Molecular analysis identified two isolates, CPV-Gannavaram and CPV-Garividi, showing 100% and 98.47% nucleotide identity to reference CPV1 strains, respectively. Phylogenetic analysis clustered both isolates within the genus *Lambdapapillomavirus*. Sequence alignment revealed high conservation in the central L1 motifs, though the local variants exhibited a divergence from CPV-6. B-cell epitope prediction identified a high-probability immunogenic region within the conserved L1 fragment. This study confirms that CPV1 is the primary etiological agent of oral papillomatosis in the sampled regions. The high genetic stability of the L1 gene and the identification of potent B-cell epitopes provide a strong foundation for the development of novel vaccines.

**Keywords:** Canine Papillomavirus, L1-Gene, B-cell Epitope, Phylogeny, Vaccine Design

### Introduction

Papillomaviruses (PVs) are small, non-enveloped viruses with a circular, double-stranded DNA genome of ~8,607 bp size (Feng *et al.*, 2025; Reis *et al.*, 2022; VanDoorslaer *et al.*, 2018; Resendes *et al.*, 2024; Luff *et al.*, 2012)<sup>[1, 2, 3, 4, 5]</sup>. PVs have been reported to caused hyperplastic and rarely neoplastic diseases in dogs (Munday *et al.*, 2022a; Munday *et al.*, 2022b)<sup>[6, 7]</sup>. In Canines the hyperplastic lesions (warts) are commonly encountered in regions which are more prone for trauma such as oral cavity, ears, face, and feet (Gould *et al.*, 2021; Lane *et al.*, 2017)<sup>[8, 9]</sup>. In severe cases the lesions may turn into exophytic or inverted papillomas due to folding of hyperplastic epithelium (Lange *et al.*, 2010; Munday *et al.*, 2017; Orlandi *et al.*, 2021)<sup>[10, 11, 12]</sup>. The papillomas may regress within 6 months irrespective of several treatment protocols. However, some papillomas may progress to persistent papillomas and squamous cell carcinomas (SQCC) (Medeiros-Fonseca *et al.*, 2023; Athulya *et al.*, 2024)<sup>[13, 14]</sup>. In rare cases the papillomas may coalesce involves large proportion of the body (Munday *et al.*, 2022c)<sup>[15]</sup>. Immune dysfunction of the host animal and certain breed predisposition are important factors for disease development (Stokking *et al.*, 2004; Luff *et al.*, 2016)<sup>[16, 17]</sup>. Persistent disease is suspected to reflect an underlying immune defect which may be indicated by the appearance of new lesions six months or more after the initial outbreak is particularly suggestive of immune dysfunction (Munday *et al.*, 2024)<sup>[18]</sup>.

Canine oral papillomas usually show characteristic features such as outward-growing (exophytic) finger-like projections, thickening of the epithelium, and increased keratin formation, which are typical indicators of CPV infection (Goldschmidt & Hendrick, 2002; Rath *et al.*, 2017; Goldschmidt & Goldschmidt, 2016a; Lange & Favrot, 2011)<sup>[19, 20, 21, 22]</sup>. Careful examination of tissue structure and cellular details is important to distinguish these benign lesions from malignant conditions like squamous cell carcinoma (Goldschmidt *et al.*, 2002; Goldschmidt *et al.*, 2016b)<sup>[19, 23]</sup>. Moreover, the presence of inflammatory cells within the tissue reflects the host's immune response to the viral infection (Rath *et al.*, 2017; Maglennon *et al.*, 2011)<sup>[20, 24]</sup>.

The coding region of PVs comprises six to eight open reading frames: the early genes code for five to seven early proteins (E1, E2, E4, E5, E6, E7, E8) and the late structural genes code for structural proteins L1, L2 (Bernard *et al.*, 2010; Chang *et al.*, 2020; McBride, 2017)<sup>[25, 26, 27]</sup>. The genes encoding E1, E2 and E4 are involved in efficient DNA replication, Transcription and initiation of viral replication (Maglennon *et al.*,

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2011)<sup>[24]</sup>. The E5, E6 and E7 proteins are pathologically significant, alter the replication and differentiation of an infected cell by preventing the keratinocytes from becoming post-mitotic, induces the cell division and inhibits apoptosis (Doorbar *et al.*, 2012; VandePol *et al.*, 2013; Doorbar, 2013)<sup>[28, 29, 30]</sup>. The L1 and L2 genes encode for capsid proteins of the virus and expressed when the infected cell is nearer to the skin surface (Longworth *et al.*, 2004)<sup>[31]</sup>. The L1 locus encodes the major capsid protein that constitutes most of the virion and underpins current PV vaccine design. Based on the highly conserved nucleotide sequence of the L1 gene, the PVs are classified into genera, species, and types. The PVs with greater than 60% nucleotide identity, usually classified within the genus, the PVs greater than 70% similarity are within the same species and PVs with more than 90% identity are belonging to the same type (de Villiers *et al.*, 2004; VanDoorslaer *et al.*, 2017; Bernard *et al.*, 2010; Lange & Favrot, 2011)<sup>[32, 33, 25, 22]</sup>. So far, 26 *Canis familiaris Papillomaviruses* (CPVs) have been characterized genetically, and classified under one of the four genera: *Lambdapapillomavirus* genus contains types CPV1 and CPV 6, that cause papillomas; *Taupapillomavirus* – types 2, 7, 13, 17 and 19; *Chipapillomavirus* - types 3, 4, 5, 8, 9, 10, 11, 12, 14, 15, 16, and 20) and *Omegapapillomavirus* – contains novel papillomavirus of dogs CPV- 26 recently identified (Munday *et al.*, 2017; Tisza *et al.*, 2016; Munday *et al.*, 2024)<sup>[11, 34, 18]</sup>.

Many studies show that the L1 protein can self-assemble into structures resembling the native papillomavirus surface while retaining immunogenicity, making it a key target for recombinant vaccines against oncogenic PVs (Buck *et al.*, 2013; Abdul-Zahra *et al.*, 2025)<sup>[35, 36]</sup>. Identifying minimal antigenic regions that elicit immune responses, known as B-cell epitopes, remains a major challenge in peptide-based vaccine design, necessitating accurate prediction methods (Singh *et al.*, 2013)<sup>[37]</sup>. Reliable computational tools such as BepiPred-2.0, which is based on high-quality crystal structure derived epitope data, offer improved predictive accuracy compared to earlier methods available through the IEDB Analysis Resource (Jespersen *et al.*, 2017; Aqsha *et al.*, 2023; Mahmoudvand *et al.*, 2022)<sup>[38, 39, 40]</sup>. Such predicted epitopes can be further evaluated for antigenicity, conservancy, and immunogenic potential, thereby contributing to the design of broadly protective and cost-effective vaccines against papillomavirus infections (Patronov *et al.*, 2013)<sup>[41]</sup>.

In India, except (Ponnusamy *et al.*)<sup>[42]</sup>, till date no CPV types have been characterized and research focused solely on therapeutic approaches (Sivarama Krishna *et al.*, 2024)<sup>[43]</sup>. Herein, two adult dogs (German Shepherd and Spitz) were presented to the clinics with a history of oral papillomas. The CPV in papilloma lesions was identified in PCR by amplification of the L1 gene using specific primers. The partial sequence analysis of the L1 gene reveals its 100% nucleotide sequence identity with *Lambdapapillomavirus* types and its phylogenetic analysis reveals its close association with CPV type 1.

## Materials and methods

### Clinical case and sample collection

In the presented study two clinical cases of oral papillomatosis in Dogs were studied. Case 1: A 11 months old male German shepherd was presented to the Veterinary Polyclinic, Guntur, Andhra Pradesh, India located at coordinates of 16.3008° N, 80.4428° E, with a history of multiple proliferative oral cauliflower like growths of variable sizes in the oral cavity. Case 2: A one year old male Spitz dog was brought to the Veterinary clinical Complex, College of Veterinary Science, Garividi, Vizianagaram district, Andhra Pradesh, India located at coordinates of 18.29° N latitude and 83.56° E longitude with history of multiple irregular cauliflower like growths at junction of lower lip and the gums. In both cases, the papillomatous growth in the oral cavity was surgically excised following the animal ethical procedures. An irregular shaped papillomatous tissue of around 50 grams was sampled for histopathology and molecular typing of the isolates.

### Histopathological examination

Tissue samples were fixed in 10% neutral buffered formalin for 72 hours until adequately hardened. The fixed tissues were then placed in stainless steel tissue capsules and washed overnight under running tap water to remove excess fixative. Subsequently, the tissues were dehydrated through graded alcohol series consisting of 70%, 80%, 90%, and absolute alcohol I and II, with each step maintained for one hour. Following dehydration, clearing was carried out using two changes of xylene for 20 minutes each. The cleared tissues were then impregnated with molten paraffin wax at 56 °C with three changes, each lasting one hour, and subsequently embedded in paraffin blocks. The tissue blocks were cast in Leukhart L molds, allowed to solidify, and stored under refrigeration. For sectioning, the paraffin blocks were mounted onto the chuck of a rotary microtome (LEICA RM2125RTS) and trimmed until the blade contacted the entire tissue surface. Finally, sections of 5 µm thickness were cut and carefully transferred onto clean glass slides coated with Mayer's albumin using a fine camel hair brush, and excess moisture was gently removed using moistened blotting paper. The sections were deparaffinized by heating at 60 °C for 30 minutes, followed by three changes of xylene, spending at least one minute at each station. The sections were then rehydrated through descending grades of alcohol (90%, 80%, and 70%) for one minute each, and subsequently immersed in distilled water. The rehydrated sections were stained with haematoxylin for 15 minutes, rinsed in running water for 10–15 minutes, and counterstained with eosin for one minute. After washing with water, the slides were dehydrated using 95% alcohol followed by two changes of absolute alcohol, and then cleared in xylene. Finally, the sections were mounted with Distyrene Tricresyl Xylene (DPX) mountant. The prepared slides were subsequently examined and photographed under a compound microscope for histopathological evaluation.

### Extraction of DNA from papillomas

Twenty grams of the oral wart tissue was triturated with 500 µL of sterile phosphate-buffered saline (PBS), pH 7.2 using a sterile mortar and pestle and the resultant homogenate was transferred into a fresh tube. The sample was incubated in boiling water for 10 minutes, followed by snap chilling. This sample was centrifuged at 8,000 rpm for 5 minutes at 4 °C, and the supernatant was collected. The supernatant was mixed with an equal volume of phenol (200 µL) and chloroform (200 µL), vortexed, and incubated at room temperature for 5 minutes. The mixture was then centrifuged at 10,000 rpm for 5 minutes at 4 °C, and the aqueous phase was transferred into a fresh tube. To the aqueous phase, 700 µL of isopropanol was added, incubated at room temperature for 5 minutes, and centrifuged at 14,000 rpm for 10 minutes at 4 °C. The supernatant was discarded, and the pellet was washed with 500 µL of 70% ethanol, followed by centrifugation at 14,000 rpm for 5 minutes at 4 °C. The supernatant was discarded, and the pellet was air-dried, resuspended in 40 µL of nuclease-free water and stored at –20 °C until further use. Extracted DNA was used as a template in the PCR targeting the L1 gene of CPV.

### Standardization of PCR for amplification of L1 gene

The L1 gene of CPVs was amplified in PCR with the following L1 gene specific oligonucleotide primers of CPV: L1-F5'-CTTGTGGGGCTTAAGAGG-3' and CPV L1-R 5'-TGCAGTGTGTACCTGTCCTG-3' (Teifke *et al.*, 1998; Brandes *et al.*, 2009)<sup>[44, 45]</sup> with an amplicon size of 261 bp. The amplification was performed using Genei Red dye Master mix (602100011730) using ProFlex PCR system from Applied Biosystems Thermal cycler. The reaction was standardized with an initial denaturation at 95 °C for 5 min, followed by 35 cycles of 94 °C for 1 min, 55.5 °C for 30 sec, 72 °C for 2 min and final extension at 72 °C for 10 min. Amplicons were resolved on 1.5% agarose gel and analysed in a Bio-Rad gel documentation system.

### Sequencing and typing of CPV

The amplified products of L1 gene of CPV were sequenced by Sanger dideoxy sequencing method in an automated sequencer at Barcode Biosciences Private Limited, Bangalore, India. Forward and reverse reads were assembled in BioEdit to produce consensus sequences, using reference sequences from the NCBI database. The partial sequences were analysed in BLAST, NCBI website and the type of the CPV were identified based on the percent nucleotide identity. The sequences were aligned with the available CPV sequences from the NCBI, using Multiple sequence alignment tool in MEGA 12.0 with Clustal W program. The sequence identity between the isolates under study and its closest relatives in the genus *Lamdapapillomavirus* were deduced in multiples sequence alignment.

### Phylogenetic analysis

The phylogenetic analysis was performed by Maximum likelihood method and Tamura Nei model of nucleotide substitutions using MEGA 12.0 tool and the tree with the highest log likelihood was generated. The analytical procedure encompassed 28 coding sequences of L1 gene from 26 identified CPV types. The phylogenetic tree was analysed and identified the ancestral relationship between the isolates under study and other CPV types.

### In-silico linear B-cell epitope prediction

To evaluate the immunogenic potential of the L1 major capsid protein from the Garividi and Gannavaram isolates, linear B-cell epitope prediction was performed on the amino acid sequences. The primary sequence of the L1 protein fragment (approximately 85 amino acids) was analysed using the BepiPred-2.0 algorithm, hosted on the IEDB (Immune Epitope Database) server. BepiPred-2.0 utilizes a Random Forest algorithm trained on epitopes determined from crystal structures, providing superior predictive power for identifying residues likely to be recognized by B-cells (Jespersen *et al.*, 2017)<sup>[38]</sup>. For this study, a standardized threshold of 0.500 was applied to balance sensitivity and specificity. The analysis followed these criteria: Positive Prediction: Residues with a propensity score exceeding the 0.500 threshold were classified as part of a potential linear B-cell epitope. These are represented visually as yellow peaks in the BepiPred profile. Negative Prediction: Residues falling below the threshold (green regions) were considered non-immunogenic or unlikely to elicit a B-cell response (Jespersen *et al.*, 2017; Larsen *et al.*, 2006)<sup>[38, 46]</sup>. The sequence profile was evaluated for the entire 85-residue fragment to determine the average immunogenicity score and identify high-affinity regions. The peak maximum score (0.631) and the overall sequence average (0.490) were recorded to assess the comparative immunogenic strength of the L1 fragment relative to known viral antigens.

## Results and discussion

In the present study two clinical cases of CPVs, with oral papillomatosis lesions were analysed for histopathological evaluation and molecular typing. In both cases, the case history includes profuse salivation with bad breath and difficulty in food intake with pain. Morphologically, the lesions resemble cauliflower like masses, with irregular sizes ranging from few mm to cm, greyish and white in colour with folded epithelium located in the oral cavity (Figure 1). The large sized lesion was selected for excision and histopathological examination.

### Histopathological characterization of canine oral papillomatosis

Histopathological examination of the biopsy specimens stained with Haematoxylin and Eosin (H&E) confirmed a diagnosis of Canine Oral Papilloma. The lesions exhibited classic benign neoplastic proliferation of the surface epithelium. The Architectural Features of the sections revealed marked exophytic growth characterized by multiple, complex, finger-like (papillary) projections extending from the epidermis. Each papillary frond was supported by a central, narrow fi-

brovascular core of connective tissue. The Epidermal changes reveals that there is a significant hyperplasia of the stratified squamous epithelial cells. The neoplastic cells remained well-differentiated, maintaining a clear maturation sequence from the basal layer to the stratum corneum. The Cytological detail reveals that the epithelial layers showed varying degrees of acanthosis (thickening of the spinous layer) and hyperkeratosis. Although the basal layer was hyperplastic, it remained strictly intact, with no evidence of basement membrane breach or invasive growth into the underlying dermis. The connective tissue stroma within the papillary cores showed moderate to severe infiltration of mononuclear inflammatory cells (predominantly lymphocytes and plasma cells), consistent with a localized host immune response to the viral (CPV1) challenge.

### Optimization of DNA extraction from keratinized tissue

In this study, the standard phenol-chloroform extraction method was modified to improve both the yield and purity of the genetic material. Specifically, triturated samples were subjected to a 10-minute boiling water bath to soften the fibrous tissues and facilitate cellular lysis. Comparative analysis demonstrated that this thermal pretreatment significantly enhanced the quality and quantity of the extracted DNA compared to samples processed without prior boiling, providing a superior template for subsequent PCR amplification.

### Molecular detection of CPV late genes and genotyping

The L1 gene which is the primary criterion for PV classification and a key target for vaccine design was successfully amplified from both clinical isolates. PCR using gene-specific primers (Teifke *et al.*, 1998)<sup>[44]</sup> yielded an amplicon of near 261 bp (Fig. 3), confirming the presence of CPV as the etiological agent in the sampled oral papillomas. For definitive molecular typing, the amplicons from both isolates were sequenced and subjected to comparative bioinformatic analysis. Alignment of forward and reverse reads produced a partial L1 gene sequence of 265 bp. NCBI BLAST analysis revealed high nucleotide sequence identity with established CPV strains: CPV-Gannavaram isolate (PX990886): 100% identity and CPV-Garividi isolate (PX990887): 98.47% identity. Phylogenetic and sequence identity thresholds were used to assign the isolates to the genus level. Both isolates shared >60% nucleotide identity with papillomaviruses within the genus *Lamdpapillomavirus*. Consequently, the CPV-Gannavaram and CPV-Garividi isolates were classified as Canine Papillomavirus Genotype 1 (CPV1).

The comparative analysis of the L1 protein sequences from two novel local isolates, CPV-GARIVIDI-L1 and CPV-GANNAVARAM-L1, reveals significant insights into the genetic diversity and evolution of canine papillomaviruses in the region. The multiple sequence alignment, performed using Clustal Omega (1.2.4), highlights both highly conserved domains and distinct variations between these isolates and established reference types such as CPV-6 and CPV1-MF321777.1.

### Sequence homology and conservation

The alignment demonstrates a high degree of conservation across all four sequences, particularly in the central region represented by the motifs LVWGLRGLEIGRGQPLGISVTGHPTFDLYN. The presence of asterisks (\*) in the Clustal output indicates positions with a single, fully conserved residue, which are essential for maintaining the structural integrity of the major capsid protein L1. CPV-GARIVIDI-L1 and CPV-GANNAVARAM-L1 share nearly 100% identity with each other, suggesting they belong to a closely related lineage circulating within the same geographical cluster. In contrast, CPV-6 maintains a significantly longer C-terminal tail (PPIELKNTLIQDGD...), indicating that the Garividi and Gannavaram variants may represent a distinct subtype or a novel variant with modified capsid properties.

### Phylogenetic analysis

The sequences targeting the L1 gene (the major capsid protein) were used to construct a Neighbor-Joining tree, with genetic distances represented by a scale bar of 0.10 substitutions per site. The phylogenetic tree reveals that the CPV-GARIVIDI-L1 (Accession number-

PX990887) and CPV-GANNAVARAM-L1 (Accession number-PX990886) strains are nested within a distinct and well-supported clade. Notably, these two isolates show a very high degree of genetic identity to each other, sharing a most recent common ancestor (MRCA) with the reference strain CPV1-MF321777.1. This close clustering with the CPV1 reference sequence identifies the Garividi and Gannavaram isolates as members of the Canine Papillomavirus Type 1 (CPV1) genotype.

### *In-silico linear B-cell epitope prediction*

To assess the immunogenic potential of the L1 protein fragment of the Garividi and Gannavaram isolates, the amino acid sequence was subjected to linear B-cell epitope prediction using the BepiPred 2.0 algorithm, Immune epitope data base analytical tool (Jensen *et al.*, 2018). The analysis parameters include a default threshold of 0.500 was applied. Residues with a score above this value (represented by the yellow peaks in the graph) are predicted to be part of a linear B-cell epitope, while those below (green areas) are unlikely to be immunogenic. The protein fragment analysed encompasses approximately 85 amino acids of the L1 major capsid protein. The average score for the entire sequence was 0.490, with a peak maximum of 0.631. Predicted Immunogenic Peptides

The algorithm identified three potential linear epitopes, with two of them being highly significant for diagnostic and prophylactic applications: Primary Epitope (Positions 25–49): The most prominent immunogenic region is a 25-mer peptide with the sequence TFDYNDVENPNKNLAGHGGGTDSR. This region corresponds to the highest peak in the graph (0.631), indicating a high probability of surface exposure and antibody binding. This peptide is a prime candidate for the development of a synthetic vaccine against CPV1. Secondary Epitope (Positions 71–82): A 12-mer peptide (GEHWSLTRWCTG) was also identified. Though shorter, its consistent score above the 0.5 threshold suggests it contributes to the overall antigenicity of the L1 protein. Minor Epitope (Positions 15–17): A very short 3-mer peptide (PLG) was flagged; however, due to its minimal length, it is likely of low significance for independent vaccine design.

The prevalence of CPVs varies geographically and its systematic studies are less explored in comparison to Human papillomaviruses, yet it has a potential impact on canine health. As per the swiss research on Canines detected over 50% prevalence of CPV DNA in samples collected from oral and finger like projections from healthy dogs ((Lange *et al.*, 2011)<sup>[47]</sup>). Similarly, the US based studies revealed a 5.3% of CPV DNA in canine samples. Brazil, Switzerland, South Africa and several other countries have reported a variety of CPV genotypes across canine populations (Merchioratto *et al.*, 2024; Lange *et al.*, 2009)<sup>[48, 49]</sup>. Molecular characterization studies on CPV and the prevalence of its genotypes remain a largely neglected area in the Indian subcontinent. This is highlighted by the fact that there is only one recent report of *Lambdapapillomavirus* from Tamil Nadu (Ponnusamy *et al.*, 2004)<sup>[42]</sup>. In India, the majority of research on papilloma has historically focused on the clinical and therapeutic management of lesions, rather than their molecular or genomic characterization (Sivarama Krishna *et al.*, 2024)<sup>[43]</sup>. This prioritisation of treatment outcomes has resulted in a significant knowledge gap regarding the genetic diversity and prevalence of specific genotypes within the region. This lack of genomic a directly hinders the development of targeted diagnostics and effective vaccines. To address these gaps, the present study focused on the molecular characterization and epitope prediction of CPV. By identifying these specific antigenic determinants, this research aims to provide a foundation for developing more targeted diagnostics and recombinant vaccines tailored to the strains circulating in the Indian subcontinent.

Historically, H&E staining remains an essential preliminary diagnostic tool for CPV infections, that provides basic visual impact on assessment of characteristic cytopathic alterations in CPV lesions. Histopathological analysis in this study confirms the benign neoplastic nature of canine oral papillomas. The observed epithelial hyperpla-

sia, exophytic papillary projections, and prominent fibrovascular cores reflect organized keratinocyte proliferation induced by viral infection (Goldschmidt *et al.*, 2002; Lange *et al.*, 2011)<sup>[19, 22]</sup>. In general, the appearance of koilocytes-keratinocytes exhibiting peri nuclear halos and nuclear pleomorphism, is a diagnostic hallmark of papillomavirus infections. Occasionally, Intranuclear inclusions may be present within keratinocytes (Narama *et al.*, 2005; Chang *et al.*, 2020; Orlandi *et al.*, 2023)<sup>[50, 26, 51]</sup>. This response is typically mediated by viral oncoproteins E6 and E7, which disrupt cell cycle regulation and inhibit apoptosis (Doorbar *et al.*, 2012)<sup>[28]</sup>. While acanthosis and hyperkeratosis indicate sustained viral influence on epithelial differentiation, the intact basement membrane and orderly maturation distinguish these lesions from invasive malignancies like squamous cell carcinoma (Munday *et al.*, 2022a; Goldschmidt *et al.*, 2002)<sup>[6, 19]</sup>. However, the H&E stain offers only the morphological insights, inherently it is non-specific and cannot identify the genotype of the CPV involved. Ultimately the PCR was employed in conjunction with H&E staining for diagnostic accuracy (Luff *et al.*, 2012; Munday *et al.*, 2023)<sup>[5, 52]</sup>.

Polymerase Chain Reaction (PCR) remains the gold standard for detecting CPV DNA, facilitating both genotyping and the molecular characterization of viral oncoproteins (Wang *et al.*, 2010)<sup>[53]</sup>. In this study, we utilized consensus primers targeting a highly conserved 265 bp segment of the L1 gene, which encodes the major capsid protein (Yuan *et al.*, 2012; Kovanda *et al.*, 2011)<sup>[54, 55]</sup>. Because the L1 open reading frame (ORF) is the most conserved region across the *Papillomaviridae* family, its nucleotide sequence identity is the primary criterion for taxonomic classification and genotype identification (Orlandi *et al.*, 2022; Resendes *et al.*, 2024)<sup>[12, 4]</sup>. The primers used in this study specifically amplified the 265 bp product in both Gannavaram and Garividi samples, confirming the presence of CPV DNA (Fig No.4). Besides these several universal or broadly reactive primers have been available and employed for genotyping of PVs, yet their application in typing all 26 CPV genotypes is need to be validated further (Luff *et al.*, 2012; Chang *et al.*, 2020; Lange *et al.*, 2011)<sup>[5, 26, 47]</sup>. Nucleotide BLAST analysis of the 265 bp L1 gene fragments revealed 99–100% sequence identity with established Canine Papillomavirus Type 1 (CPV-1) reference strains. This high degree of genetic stability confirms their classification within the genus *Lambdapapillomavirus* and aligns with the expected etiology of canine oral papillomatosis. Our findings are highly consistent with the recent report by Ponnusamy *et al.*, 2004<sup>[42]</sup>, which similarly identified CPV-1 in a Rottweiler from Tamil Nadu. The near-perfect sequence identity between our isolates and the Tamil Nadu strain suggests that a highly conserved CPV-1 lineage is circulating across different regions of the Indian subcontinent. : This consistency reinforces the reliability of targeting the L1 gene for regional diagnostics and suggests that vaccines developed against these conserved strains would likely be effective across diverse geographic locations in India. Previous research has demonstrated that the detection of the L1 gene in CPV samples serves as a marker for active productive infection (Beckwith-Cohen *et al.*, 2015; Howley *et al.*, 2013)<sup>[56, 57]</sup>. Since L1 encodes the major capsid protein, its presence typically coincides with the late stage of the viral life cycle, during which virion assembly occurs within the upper layers of the epithelium.

### *Divergence from CPV-6*

Phylogenetic analysis of the L1 gene using the Neighbor-Joining method confirmed that the CPV-GARIVIDI-L1 (PX990887) and CPV-GANNAVARAM-L1 (PX990886) isolates cluster within a well-supported clade alongside the reference strain CPV1-MF321777.1. This close clustering, with a scale bar of 0.10 substitutions per site, definitively identifies these isolates as members of the Canine Papillomavirus Type 1 (CPV1) genotype (Yuan *et al.*, 2012; Orlandi *et al.*, 2022)<sup>[54, 12]</sup>. While CPV-6 is the closest evolutionary neighbor (as seen in phylogenetic tree), the MSA highlights specific regions of genetic divergence. There are several "mismatched" columns where CPV-6 differs from the CPV-1/Garividi/Gannavaram cluster. These

differences justify the classification of CPV-1 and CPV-6 as distinct genotypes, even though they both belong to the genus *Lambdapapillomavirus*. The long stretches of identical nucleotides (especially between positions 60–120 and 180–230) represent highly conserved regions of the L1 gene. These regions are ideal targets for the gene-specific primers (Teifke *et al.*, 1998)<sup>[44]</sup> used in PCR assays. The topology of the tree demonstrates significant genetic diversity among the 26 types of CPV represented. The nearest evolutionary neighbor to the Garividi-Gannavaram-CPV1 cluster is CPV-6. This indicates that while CPV1 and CPV6 share a common lineage, they have diverged significantly enough to be classified as separate types.

### ***In-silico prediction of B-cell epitopes on L1 protein of CPV1***

The PVs are responsible for 27–30% of different cancers in a wide variety of the animals (Van Doorslaer, 2022; Dorttas *et al.*, 2020)<sup>[58, 59]</sup>. Interestingly the PVs are highly species specific. While CPV-induced neoplasia is considered relatively rare compared to other canine skin tumors, the presentation of multiple oral papillomas observed in this study aligns with numerous clinical reports (Munday *et al.*, 2016)<sup>[60]</sup>. It is important to note that CPV-1 has been associated with persistent oral papillomatosis, which carries a documented risk of progression to Squamous Cell Carcinoma (SCC) (Regalado Ibarra *et al.*, 2018; Goldschmidt *et al.*, 2002)<sup>[61, 19]</sup> Furthermore, viral plaques induced by other CPV genotypes have also been reported to undergo malignant transformation into SCC (Luff *et al.*, 2016; Munday *et al.*, 2022a)<sup>[17, 6]</sup>. This potential for progression underscores the clinical significance of early molecular identification and monitoring of persistent lesions. The L1 capsid protein harbours the Major immunogenic component, that can be targeted for development of novel vaccines (Hainisch *et al.*, 2017)<sup>[62]</sup>. Previous studies with Human Papillomaviruses have reported that the conserved amino acid sequences within the epitopes are crucial for vaccine development (Cetina-Cetz *et al.*, 2022)<sup>[63]</sup>.

The in-silico characterization of the L1 protein fragments from the Garividi and Gannavaram isolates confirmed their immunogenic potential through the identification of three linear B-cell epitopes. Within the conserved 85-amino acid sequence, the most prominent immunogenic region was identified as a 25-mer peptide (TFDRYNDVENPNKNLAGHGGGTDSSR) spanning positions 25–49. This region exhibited the highest surface exposure and antibody-binding probability (peak score of 0.631), marking it as a primary immunodominant candidate for vaccine development. A secondary 12-mer epitope (GEHWSLTRWCTG) at positions 71–82 was also identified, likely contributing to the overall antigenicity of the L1 capsid. While a third minor epitope was predicted, its short length (three amino acids) suggests limited functional significance in eliciting a robust immune response. These findings align with the role of the major

capsid protein as the target for neutralizing antibodies, providing a molecular basis for the design of recombinant subunit vaccines tailored to the CPV-1 strains circulating in the Indian subcontinent. Consistent with our findings, in-silico B-cell epitope prediction has been successfully applied to the L1 capsid proteins of Bovine Papillomaviruses (BPV) and Human Papillomaviruses (HPV) in several recent studies (Modis *et al.*, 2002; Kumar *et al.*, 2022; Sylvere *et al.*, 2025; Lee *et al.*, 2024)<sup>[64, 65, 66, 67]</sup>. The identification of these specific epitopes on the CPV L1 capsid represents a significant step forward in developing novel diagnostics and broad-spectrum recombinant vaccines tailored to the Indian subcontinent.

However, further research including Molecular Dynamics (MD) simulations and structural characterization—is required to assess the structural stability, flexibility, and dynamic atomic interactions of these predicted peptides. Such data will be crucial for validating their immunogenic efficacy in vivo and ensuring the development of stable, high-affinity antigenic candidates for clinical use.

### **Conclusion**

This study provides a multi-faceted characterization of Canine Papillomavirus Type 1 (CPV1) isolates from oral papillomatosis cases in the Vizianagaram and Krishna districts. Our findings confirm that the classic "cauliflower-like" oral lesions are associated with a benign neoplastic proliferation of the squamous epithelium, characterized by marked exophytic papillary growth and mononuclear inflammatory infiltration, consistent with a localized host immune response. Molecular typing and phylogenetic analysis confirmed that the CPV-Gannavaram and CPV-Garividi isolates belong to the genus *Lambdapapillomavirus*. The high sequence identity (98.47–100%) between these local isolates and reference strain CPV1-MF321777.1 indicates a stable circulating lineage in the region. The in-silico linear B-cell epitope prediction using BepiPred 2.0 successfully identified high-probability immunogenic residues within the L1 major capsid protein. The peak score of 0.631 within the conserved central motifs suggests that these fragments are strong candidates for the development of synthetic peptide or recombinant subunit vaccines.

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### **Conflicts of interest**

The authors declare that there are no conflicts of interests that could inappropriately influence the findings of this work.

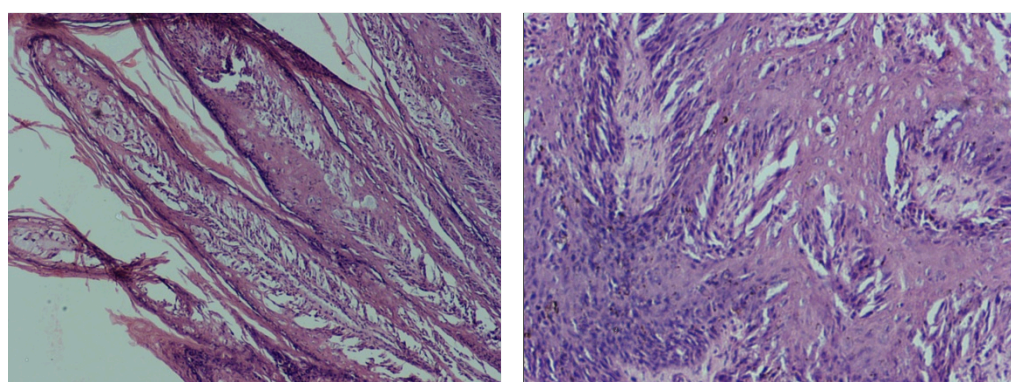
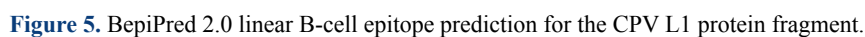
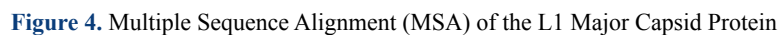


**Figure 2.** Histopathological section of a canine oral papilloma (H&E, [Insert Magnification, e.g., 100x]).



Gross morphological appearance of viral-induced oral lesions in a German Shepherd and a Spitz dog.

The evolutionary relationship of CPV-GARIVIDI-L1 and CPV-GANNAVARAM-L1 isolates relative to established CPV types (CPV-1 to CPV-26). The phylogenetic tree was constructed using the

Neighbor-Joining method based on the partial L1 capsid protein sequences.

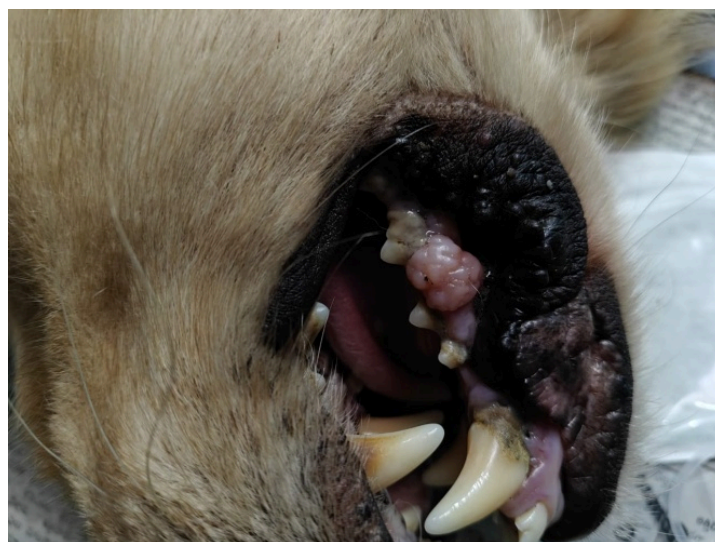


Fig: 1 Clinical Presentation of Oral Papillomatosis in Two Canine Patients

Comparative alignment of the amino acid sequences of the L1 protein fragment from CPV-GARIVIDI-L1 and CPV-GANNAVARAM-L1 isolates against reference sequences CPV-6 and CPV1-MF321777.1.

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