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# Increased Detection of Merkel Cell Polyomavirus in Non-Melanoma Skin Cancer and Its Association with Host Immunogenetic Profile

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**Abstract: Background:** Merkel cell polyomavirus (MCPyV) has been established as an etiological agent in Merkel cell carcinoma (MCC), yet its role in other cutaneous neoplasms remains under investigation. In the context of non-melanoma skin cancer (NMSC), the influence of host immunogenetics on MCPyV persistence is poorly understood. **Objective:** To investigate the presence of MCPyV in various skin lesions, particularly NMSC, and its association with cytokine gene polymorphisms related to immune regulation. **Methods:** We analyzed 274 skin biopsies (lesional, perilesional, and healthy skin) from 84 patients undergoing dermatological evaluation. MCPyV DNA and polymorphisms in IL-6, IL-10, IFN-γ, and TNF-α genes were detected using PCR-based assays. **Results:** MCPyV was significantly more prevalent in NMSC and non-malignant lesions than in surgical margins or healthy skin ($p = 0.050$ and 0.048, respectively). Concordance between lesion and margin samples was low ($\kappa = 0.305$), suggesting microenvironment-specific viral persistence. Notably, high-expression IL-10 genotypes (-1082GG) and low-expression IL-6 genotypes (-174AA) were significantly associated with MCPyV detection ($p = 0.048$ and $p = 0.015$, respectively). **Conclusion:** MCPyV preferentially localizes to NMSC lesions, particularly in individuals with immunogenetic profiles favoring viral persistence. Given the unclear role of MCPyV in NMSC pathogenesis, our findings call for comprehensive studies to determine whether the lesional environment facilitates viral persistence or reflects a more complex viral–host interaction with potential implications in cutaneous oncogenesis.

**Keywords:** Merkel cell polyomavirus; non-melanoma skin cancer; immunogenetics

## 1. Introduction

Non-melanoma skin cancer (NMSC) is the most prevalent malignancy worldwide, with basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) constituting the majority of cases [1]. While cumulative ultraviolet (UV) radiation exposure is a well-established risk factor, other contributors, including viral infections, are under investigation [2]. Among these, Merkel cell polyomavirus (MCPyV) has been implicated in Merkel cell carcinoma (MCC) [3] and has been detected in various skin lesions, suggesting a possible role in NMSC pathogenesis [4].

The presence of MCPyV in both malignant and non-malignant skin lesions raises questions about its involvement in skin carcinogenesis [5]. However, the mechanisms underlying MCPyV's interaction with host immunity, particularly concerning cytokine gene polymorphisms, remain

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largely unexplored [6]. Cytokines such as interleukin-6 (IL-6), interleukin-10 (IL-10), interferon-gamma (IFN-γ), and tumor necrosis factor-alpha (TNF-α) play critical roles in immune regulation, inflammation, and tumor progression [7]. Polymorphisms in these cytokine genes can influence their expression and have been associated with susceptibility to various infectious diseases and cancers [8,9]. However, to our knowledge, no previous study has investigated the genetic profile of cytokines in relation to MCPyV detection in skin lesions, making this the first study to explore this immunogenetic association in this context.

This study aims to investigate the presence of MCPyV in different skin lesions and its association with cytokine gene polymorphisms. By analyzing paired lesion and surgical margin samples, we aim to assess the consistency of viral detection across different skin compartments. Our findings may elucidate the potential role of MCPyV as a co-factor in skin lesion development and highlight the importance of host immunogenetics in viral persistence and skin disease susceptibility [10].

## 2. Materials and Methods

### *2.1. Patients*

A cross-sectional study was conducted using 274 fresh-frozen biopsies from 84 patients attended by the Dermatological Service of Antônio Pedro University Hospital, Fluminense Federal University, Brazil, between January 2017 and May 2021. All biopsies had clinical indications for histopathological diagnosis. The samples included lesion biopsies, biopsies from perilesional tissue, and healthy skin samples. Perilesional biopsies, later confirmed 'clear of lesional tissue' by histopathology, were obtained from tissue surrounding lesions to serve as controls for comparison, and healthy skin samples were obtained when needed to close surgical incision.

Among the 84 patients included in the study, the most frequent diagnosis was non-melanoma skin cancer (NMSC), detected in 63 patients (75.0%), with basal cell carcinoma (BCC) in 56 cases (66.7%) and squamous cell carcinoma (SCC) in 7 cases (8.3%). The remaining 21 patients (25.0%) presented with non-malignant lesions, which included premalignant (Bowen's disease and actinic keratosis), benign (cysts, lipomas, fibroma, pilomatricoma, and poroma), and inflammatory conditions (hidradenitis). The 274 samples collected in this study were classified into four categories: non-melanoma skin cancer (NMSC, 93 samples, 33.9%); non-malignant skin lesions (29 samples, 10.6%); surgical margin (95 samples, 34.7%) and healthy skin (57 samples, 20.8%).

All individuals provided written informed consent, and the study was conducted in accordance with ethical guidelines and institutional regulations. Data on age, gender, ethnicity, and tumor location were collected during the medical examiner interview. Ethnicity, classified as 'white' or 'non-white', was defined by the dermatologist according to patients phototype. Tumor location was used to infer solar exposure (high, moderate, or low) [11]. Histopathological diagnosis of all lesions was performed by the Department of Pathology of HUAP-UFF. This study was approved by the University's Ethics Committee.

### *2.2. Molecular Diagnosis of MCPyV and Cytokine Genotpyping*

All samples were fragmented and digested with proteinase K (Promega®—Madison, USA), and DNA was extracted utilizing a commercial kit following manufacturer's instructions (RTP® DNA/RNA Kit – Molecular Stratec Biomedical – Berlin, Germany). MCPyV detected by TaqMan® qPCR assays based on protocols described previously [12]. The beta-globin gene was also amplified as IC.

Extracted DNA from samples were also used for the investigation of SNPs in the promoter region of the following cytokine genes: IFN-γ (+874A>T) (rs2430561) [13], IL-6 (-174G>C) (rs1800795) and TNF-α (−308G>A) (rs1800629) [14] and IL-10 (−1082G>A (rs1800896), −819C>T (rs1800871) and −592C>A, (rs1800872) [15]. Genotyping was carried out by amplification refractory mutation system-polymerase chain reaction (ARMS-PCR) by SYBR-green® qPCR technique.

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*2.3. Statistical Analysis*

All statistical analyses were performed using IBM SPSS Statistics (version 29). Descriptive statistics were used to summarize the data, including absolute and relative frequencies for categorical variables. Measures of central tendency were calculated for continuous variables when applicable. For comparisons between groups, Pearson's chi-square test or the Fisher's exact test (when expected frequencies were low) were applied to assess associations between categorical variables. The McNemar test was used to evaluate paired concordance between lesion and surgical margin samples. Additionally, the Kappa coefficient was calculated to measure the level of agreement in viral detection across paired samples. The significance level of $p < 0.05$ was considered statistically significant for all analyses.

## 3. Results

*3.1. MCPyV Detection by Age, Sex, Ethnicity, and Lesion Type*

A total of 84 patients were included in this study (Table 1). The mean age was 67 years (range: 17–91 years), and patients were distributed across gender and ethnicity categories. The detection rate of MCPyV did not significantly differ between male and female patients ($p = 0.224$), ethnic groups ($p = 0.749$) or age ($p = 0.354$). Regarding histopathological classification, MCPyV detection varied between lesion types, but no significant differences were observed among non-malignant lesions, squamous cell carcinoma (SCC), and basal cell carcinoma (BCC) ($p = 0.674$).

**Table 1.** Frequency of MCPyV according to patients' characteristics (N=84).

| Variable | N (%) | MCPyV detection (%) | P value |
|---|---|---|---|
| **Gender** | | | |
| *Male* | 44 (52.4) | 53.2 | 0.224 |
| *Female* | 40 (47.6) | 46,8 | |
| **Ethnicity** | | | |
| *White* | 70 (85.4) | 39.7 | 0.749 |
| *Non-white* | 14 (14.6) | 45.5 | |
| ***Age** [mean yr. (range)]* | 67 (17-91) | - | 0.354 |
| **Skin lesion** | | | |
| *BCC* | 56 (66.7) | 38.2 | |
| *SCC* | 7 (8.3) | 42.9 | 0.674 |
| *Non-malignant* | 21 (25) | 50 | |

MCPyV: Merkel cell Polyomavirus; BCC: basal cell carcinoma; SCC: squamous cell carcinoma.

*3.2. Variability of MCPyV Detection According to Tissue Source and Sun Exposure*

Of the 274 skin samples obtained, we investigated MCPyV detection in relation to solar exposure, sample type, and paired concordance between lesion and surgical margin (Table 2). When analyzing solar exposure, MCPyV detection was higher in lesions with high sun exposure compared to those with moderate and low exposure. However, this difference was not statistically significant ($p = 0.159$). Pairwise comparisons showed that MCPyV detection was significantly higher in NMSC samples compared to surgical margin samples ($p = 0.050$) and healthy skin ($p = 0.048$), while no significant differences were observed between other groups. Additionally, when non-malignant and NMSC samples were combined and compared to surgical margin samples, MCPyV detection remained significantly higher ($p = 0.022$; data not shown). The analysis of MCPyV detection in paired lesion and surgical margin samples revealed a significant discordance between the two sites ($p=0.009$; Cohen's Kappa coefficient ($\kappa = 0.305$, $p < 0.0001$), suggesting that the presence of MCPyV in the lesion is not strongly predictive of its presence in the surrounding tissue. Specifically, some samples were

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positive in the lesion but negative in the margin, while others showed the opposite pattern, albeit less frequently.

**Table 2.** Detection of MCPyV in skin samples (n=274) according to solar exposion and type of sample and detection concordance.

| Category | MCPyV + | MCPyV – |
|---|---|---|
| **Solar exposure** | | |
| *Low* | 4 (25.0%) | 12 (75.0%) |
| *Moderate* | 8 (29.6%) | 19 (70.4%) |
| *High* | 45 (42.9%) | 60 (57.1%) |
| **Type of sample** | | |
| *Surgical margin*[a] | 21 (23.3%) | 69 (76.7%) |
| *Healthy skin*[ab] | 16 (31.4%) | 35 (68.6%) |
| *NMSC*[bc] | 33 (37.5%) | 55 (62.5%) |
| *Non-malignant lesions*[bc] | 11 (44.0%) | 14 (56.0%) |
| **Paired concordance**[1] | | |
| *Overall agreement* | 13 (15.1%) | 47 (54.7%) |

[1]p=0.009 (lesion vs. surgical margin); cp=0.050 (surgical margin vs NMSC) and p=0.048 (surgical margin vs non – malignant lesions). MCPyV: Merkel cell Polyomavirus; NMSC: non-melanoma skin cancer.

### *3.3. Association Between MCPyV Detection and Cytokine Gene Polymorphisms*

The analysis of MCPyV detection across different cytokine loci revealed significant variations according to genetic expression profiles. For IL-10 (1082), a significant difference was observed when comparing the high-production genotype (GG) against the combined low (AA) and medium (GA) production genotypes (p = 0.048). Regarding IL-6 (174), MCPyV detection varied significantly among genotypes. The high-production genotype (GG) differed significantly from the low-production genotype (AA) (p = 0.015). Additionally, a significant difference was found between the low (AA) and medium (GA) production genotypes (p = 0.002). For IL-10 (592 and 819), IFN-$\gamma$ (874) and TNF-$\alpha$ (308), no statistically significant associations were observed.

When analyzing the association between IL-10 (1082) genotypes and MCPyV detection specifically in NMSC samples, the high-production genotype (GG) was significantly more frequent in MCPyV-positive cases compared to the combined medium- and low-production genotypes (p = 0.0126; data not shown). No significant associations were observed for the other cytokine gene polymorphisms in relation to MCPyV detection in NMSC.

**Table 3.** Relative frequency (%) of MCPyV detection in skin samples according to cytokine expression profile.

| Cytokine (locus) | Genotype (expression) | MCPyV + | MCPyV - |
|---|---|---|---|
| *IL10 (592)* | CC *(high)* | 31.5% | 68.5% |
| | AA *(low)* | 71.4% | 28.6% |
| | CA *(medium)* | 30.4% | 69.6% |
| *(819)* | *CC* (high) | 22.2% | 77.8% |
| | TT (low) | 20.0% | 80.0% |
| | CT (medium) | 33.5% | 66.5% |
| *(1082)* | GG *(high)*[a] | 42.2% | 57.8% |
| | AA *(low)*[b] | 17.6% | 82.4% |
| | GA *(medium)* | 29.5% | 70.5% |
| *IFN (874)* | TT *(high)* | 22.6% | 77.4% |
| | AA *(low)* | 28.3% | 71.7% |
| | TA *(medium)* | 35.8% | 64.2% |
| *IL6 (174)* | GG *(high)*[c] | 38.9% | 61.1% |
| | AA *(low)*[de] | 100.0% | 0.0% |

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| Cytokine (locus) | Genotype (expression) | MCPyV + | MCPyV - |
|---|---|---|---|
| | GA *(medium)*[f] | 28.0% | 72.0% |
| *TNF (308)* | AA *(high)* | 33.3% | 66.7% |
| | GG *(low)* | 41.6% | 58.4% |
| | AG *(medium)* | 32.9% | 71.4% |

[ab] p = 0.048 (GG vs AA and GA); [cd] p = 0.015 (GG vs AA); [ef] p = 0.002 (GA vs AA). MCPyV: Merkel cell Polyomavirus.

## 4. Discussion

This study investigated MCPyV detection in different skin lesions and its association with cytokine gene polymorphisms, while also evaluating paired concordance between lesion and surgical margin samples. Our findings revealed significant differences in viral detection across tissue types, suggesting that MCPyV is more frequently detected in lesional skin, particularly in NMSC, than in surrounding non-lesional tissue. Additionally, we observed specific cytokine polymorphisms influencing viral detection patterns, reinforcing the role of host immune response in viral persistence and clearance.

The presence of MCPyV was significantly higher in NMSC and non-malignant lesions than in surgical margin and healthy skin samples. Additionally, paired analysis of lesions and surgical margins showed a significant discordance in viral detection ($p = 0.009$), with a low agreement ($\kappa = 0.305$, $p < 0.0001$). These findings indicate that MCPyV presence in the lesion does not strongly predict its presence in adjacent tissue, suggesting that the lesional microenvironment may play a role in viral persistence. One possible explanation is that the immune landscape of the lesion differs from that of surrounding skin. Malignant and premalignant skin lesions often exhibit local immunosuppression, which could facilitate MCPyV persistence, whereas surrounding tissue may have a more effective antiviral immune response, leading to viral clearance. This hypothesis is supported by studies showing that MCPyV is frequently integrated into the host genome in Merkel cell carcinoma but is often transiently detected in normal skin [3,6]. Further research is needed to determine whether MCPyV detected in NMSC lesions is episomal or integrated and how the immune environment regulates its presence.

Regarding sun exposure, MCPyV was more frequently detected in lesions with high sun exposure compared to moderate and low exposure, although this difference was not statistically significant ($p = 0.226$). This finding is consistent with reports suggesting that UV radiation is not directly linked to MCPyV presence but may contribute to viral-driven oncogenesis through immunosuppression and DNA damage [6]. Some studies have hypothesized that MCPyV reactivation may be favored by UV-induced local immune modulation, potentially explaining the higher detection in sun-exposed areas, [7,16]. Previously, we observed a significant association between MCPyV detection and UV exposure ($p = 0.010$), supporting the hypothesis of UV radiation acting as a co-carcinogen in viral-associated oncogenesis [17]. The discrepancy between these findings may reflect differences in sample size, tissue types, or methodological approaches across studies. Future research with larger cohorts and precise viral load measurements is essential to clarify the extent and biological mechanisms of MCPyV interaction with UV radiation in skin carcinogenesis.

Recent literature provides important context to our findings. Previous studies have shown frequent MCPyV detection in diverse NMSC lesions, supporting a potential viral role in skin carcinogenesis [5]. Additionally, evidence indicates that MCPyV may influence the development of both malignant and benign skin lesions under specific conditions [4]. Significant differences in viral load between NMSC lesions and adjacent non-lesional tissues further suggest a localized involvement of MCPyV within lesions [18]. Collectively, these studies reinforce our observations, highlighting MCPyV's preferential detection in skin lesions and emphasizing the potential roles of the lesional microenvironment and host immune modulation in viral persistence. Nevertheless, discrepancies between studies, particularly regarding the influence of UV exposure, underline the

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complexity of host-virus interactions in NMSC pathogenesis and indicate the necessity for continued investigation.

This study also examined the role of cytokine gene polymorphisms in MCPyV detection. Notably, significant associations were found for IL-10 (-1082G>A) ($p = 0.048$) and IL-6 (-174G>C) ($p = 0.015$ and $p = 0.002$, depending on genotype comparisons), suggesting that genetic variants influencing cytokine production may affect viral persistence. IL-10 is an anti-inflammatory cytokine that plays a critical role in immune evasion by viruses [19]. Interestingly, the GG genotype at IL-10 (-1082G>A), associated with higher IL-10 production, showed a greater frequency of MCPyV detection than the other genotypes ($p = 0.048$). This finding aligns with reports suggesting that higher IL-10 expression may suppress chronic inflammation, thereby creating an immunopermissive microenvironment that facilitates viral persistence [20,21].

Regarding IL-6, we observed significant differences related to MCPyV detection among the genotypes analyzed. MCPyV was more frequently detected in individuals with the AA genotype (low IL-6 producers) compared to those with the GA and GG genotypes (intermediate and high IL-6 producers, respectively). This suggests that lower IL-6 production, which corresponds to a reduced inflammatory state, might favor viral persistence due to a less effective antiviral immune response, facilitating viral maintenance within the skin lesions [22,23]. Interestingly, TNF-$\alpha$ (-308G>A) and IFN-$\gamma$ (+874A>T) did not show statistically significant associations with MCPyV detection, suggesting that other immune pathways may be more relevant in controlling viral presence in skin lesions. Future studies should explore additional cytokines, including IL-12 and TGF-$\beta$, which have been implicated in viral immune modulation.

When analyzing patient characteristics, no statistically significant differences were observed in MCPyV detection between sexes ($p = 0.224$) or ethnic groups ($p = 0.749$). Similarly, MCPyV detection was not significantly associated with patient age, which aligns with previous studies indicating that viral presence is not restricted to a specific age group [1]. While no strong associations were found between MCPyV detection and patient demographics, these results highlight the complexity of viral persistence in skin lesions. Factors such as host immune response, viral integration status, and cumulative sun exposure over time may play a more significant role in determining MCPyV presence rather than age or sex alone.

Although our study provides important insights into MCPyV detection in skin lesions and its association with cytokine gene polymorphisms, some limitations should be considered. First, the cross-sectional design does not allow for causal inferences, meaning we cannot determine whether MCPyV contributes to lesion development or is a secondary colonizer. Second, while qPCR was used to detect MCPyV, we did not assess viral integration status or viral gene expression, which are crucial for understanding its oncogenic potential. Additionally, although our sample size is robust for this type of study, the inclusion of some patients (seven, in total) with recurrent NMSC lesions should be acknowledged. Future studies with longitudinal follow-up and a more homogeneous distribution of samples per patient may help clarify the role of MCPyV in skin lesion development.

## 5. Conclusions

This study provides new evidence that MCPyV is more frequently detected in NMSC and non-malignant lesions than in surgical margins or healthy skin and that its presence in lesions does not strongly predict its presence in surrounding tissues, suggesting that the lesional microenvironment may favor viral persistence. Moreover, specific cytokine gene polymorphisms, particularly IL-10 and IL-6, were significantly associated with MCPyV detection, indicating that host immunogenetics plays a role in viral persistence and lesion susceptibility. By demonstrating a novel association between cytokine genotypes and MCPyV detection, this study provides new insights into the immunogenetic factors involved in viral persistence in skin lesions. These findings reinforce the need for further research into cytokine-mediated inflammation and viral immune evasion in skin carcinogenesis.

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**Institutional Review Board Statement:** This study was approved by the University's Ethics Committee (protocol: 26400313.1.0000.5243).

**Informed Consent Statement:** Written informed consent has been obtained from the patients to publish this paper.

**Data Availability Statement:** The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request, respecting patient confidentiality and ethical guidelines.

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## Abbreviations

The following abbreviations are used in this manuscript:

| | |
|---|---|
| MCPyV | Merkel cell polyomavirus |
| NMSC | Non-melanoma skin cancer |
| qPCR | Real-time PCR |
| BCC | Basal cell carcinoma |
| SCC | Squamous cell carcinoma |
| MCC | Merkel cell carcinoma |
| IL-6 | interleukin-6 |
| IL-10 | Interleukin-10 |
| TNF-$\alpha$ | tumor necrosis factor-alpha |
| IFN-$\gamma$ | interferon-gamma |

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