Electronic Journal of Medical Research
https://ejmr.respublishers.com
ISSN: 3106-1362/3106-1370

Review article

The 30-bp Deletion in the LMP1 Oncogene as a Diagnostic and Prognostic Biomarker in Nasopharyngeal Carcinoma: A scoping review

Aseel Yousef Moussa Al-Hussien [1,*] and Abdulrahman Alrayyes [2]

[1] Department of Medical Lab Sciences, Zarqa University, Zarqa, Jordan
[2] Faculty of Allied Medical Sciences, Al-Ahliyya Amman University, Amman, Jordan

*Correspondence: breakyaseel@gmail.com

Article information:
Received: 14-10-2025
Revised: 17-11-2025
Accepted: 17-11-2025
Published: 18-11-2025

Academic Editor:
Dr. Naveed Ahmed

Keywords:
Cancer
Oncogenic viruses
Critical patients
Genetic mutations
Oncogene

Abstract: Nasopharyngeal carcinoma (NPC) is a malignancy with a distinct geographical and ethnic distribution, strongly associated with the Epstein-Barr virus (EBV). The latent membrane protein 1 (LMP1) is a key EBV oncogene critical in the pathogenesis of NPC. A common 30-base pair (bp) deletion in the LMP1 gene has been identified and is postulated to enhance the oncogenic potential of the virus. This review aims to synthesize and evaluate the existing evidence on the clinical significance of the 30-bp deletion in LMP1 as a potential diagnostic and prognostic biomarker. Current evidence indicates a high prevalence of the LMP1 30-bp deletion variant in NPC tumors. The literature suggests that this genetic variant is associated with more advanced tumor stages, increased risk of metastasis, and poorer overall survival, underscoring its strong prognostic value. The accumulated data robustly position the LMP1 30-bp deletion as a highly promising molecular biomarker for NPC. Its integration into the clinical workflow could significantly improve risk stratification, guide personalized treatment strategies, and enhance patient management.

Article citation: Al-Hussien, A.Y.M., Alrayyes, A. The 30-bp Deletion in the LMP1 Oncogene as a Diagnostic and Prognostic Biomarker in Nasopharyngeal Carcinoma: A scoping review. **2025**. 1(2): 5-13. https://doi.org/10.64813/ejmr.2025.029.

Introduction

Nasopharyngeal carcinoma (NPC) is defined as a type of head and neck tumor originating from nasopharynx epithelial cells. It is a rare malignancy with an incidence below 1 per 100,000 persons per year in North America and Western countries. The most endemic region is southern China, with an incidence rate of 15 to 50 people per 100.000 per year. NPC is considered as the third most common cancer among men in South China (Ahmed et al., 2022). Asia is accounted of 85.2% for the newly registered NPC patients worldwide. In Jordan, the NPC occurs in both adults and children, where, males are more commonly affected than females with an incidence rate between 1 per 100,000 of the population (Wong et al., 2021a). According to the Jordanian Ministry of Health, the NPC percent among all cancer type in 2018 was (45, 0.6 %) cases, (28, 0.8%) of them were males and (17, 0.5%) were females (Verhoeven et al., 2018).

The TNM classification system, according to the current International Union against Cancer (UICC) and the American Joint Committee on Cancer (AJCC), is still the specific diagnostic and prognostic tool used until now. It is based on three criteria. Firstly, the site origin (T), then, the number of lymph nodes in the infected region (N), and the metastatic state (M) for distant and other regions (Guo et al., 2019). The first can choose either a letter or a number for the category T. TX denotes either no information available regarding the main tumor or its impossibility to quantify, T0 denotes the absence of any proof of a primary tumor (it cannot be located), Tis indicates that the cancer cells are not spreading into deeper layers of the cell layer; rather, they are exclusively expanding inside the layer of cells where they began. Pre-cancer or in situ cancer are other

names for Tis. A number (e.g., T1, T2, T3, or T4) following the T may indicate the extent of tumor dissemination into adjacent structures or its size. The tumor is larger and/or has invaded more adjacent tissues when the T number is higher (Lao et al., 2017). The N category can be assigned a letter or a number, NX denotes the inability to evaluate or the lack of information about the surrounding lymph nodes, N0 denotes the absence of malignancy in the lymph nodes nearby. A number (N1, N2, or N3) following the N may indicate the number, location, or size of neighboring lymph nodes that are cancer-affected. The more the cancer spread to neighboring lymph nodes, the higher the N number (Lao et al., 2017). The M category is assigned a number, M0 denotes the absence of evidence of distant cancer metastasis, M1 indicates that it has been discovered that the malignancy has spread to distant tissues or organs (Lao et al., 2017). There are some changes in the TNM classification system from the seventh edition, released in 2009 to the eighth edition, updated in 2016 according to the advancement of radiological therapy, imaging systems, and chemotherapy given to NPC patients (Guo et al., 2019). Some of these changes occurred in the T category, in which the T0 was added according to the presence of Epstein bar virus (EBV) in the cervical node despite non tumor is being identified (Guo et al., 2019).

Although it is a rare cancer, it is an aggressive type that presents with different degrees of differentiation. The undifferentiating type of NPC is the most common type found in the endemic region. NPC was found in the family cluster from a diverse population meaning that genetic factors may play a role in developing this type of cancer. It has been noted that environmental factors such as; fish and alcohol consumption, smoking, and EBV infection may play an important role in the development of NPC (Banko et al., 2016). The association between NPC and EBV began when an elevated anti-EBV IgA was noticed in NPC patients (Banko et al., 2016).

Epstein Bar Virus (EBV)

EBV is a DNA virus that affects Rosen Muller's fossa which is a layer of epithelial cells on the superior-most side in the lateral of the nasopharynx. It has a high prevalence that can cause latent infection in around 95 % of the world population (da Costa et al., 2015). Physiological changes and appearance of tumors can be seen on the site of EBV infection on both epithelial and B cells and can be occurred as a result of the expression of latent genes mainly EB-encoded early RNAs (EBER), EBV nuclear antigens (EBNA1/2/3 a, b, c), and latent membrane protein 1 or 2 (LMP1/2) (da Costa et al., 2015).

The LMP1 of EBV is a 356 amino acid integral membrane protein that has three domains: 1) a short cytoplasmic N terminal tail 2) six transmembrane alpha-helical of hydrophobic nature; and 3) a long cytoplasmic C-terminal tail. This tail has the highest activity region which is consisted of three functional domains, C-terminal activation regions 1, 2, and 3 CTAR (1, 2, and 3) (da Costa et al., 2015). The LMP1 is the first protein of EBV to have oncogenic features. Once expressed on the cell surface it will aggregate and form an activated receptor acting as a member of the tumor necrosis factors receptor (TNF-R) family that leads to different cellular signaling cascades. Some studies considered the LMP1 as a causative factor of NPC (da Costa et al., 2015). They explained this by the fact that the LMP1 acts in several ways; it causes upregulation of the A-20 gene and bcl-2 gene that leads to the inhibition of apoptosis in the infected cell, changes in the morphology of the epithelial cell, downregulation of the suppressor of metastasis, progression of angiogenesis and lead to induction of cytokines (da Costa et al., 2015). A 30-base pair deletion in the C terminal tail specifically, in CTAR2 at the end of the tail found to be a prominent polymorphism of LMP1 in EBV that increases the oncogenic features compared with prototype B95-8 LMP1. This feature is an aggressive phenotype of EBV-associated tumors. Another polymorphism was detected in the N terminal of LMP1 that led to the loss of the restriction site known as XhoI, found in NPC patients and absence in healthy individuals (Ahmed et al., 2023).

EBV is a linear double-strand DNA virus belonging to the gamma herpesvirus subfamily of Herpesviridae. It is known as humane herpesvirus 4 (HHV-4). It is considered a ubiquitous virus that infects around 95% of the world's population and causes persistent (latent) infection (da Costa et al., 2015). The main way that the infection spreads is through contact with contaminated saliva. EBV infects oropharynx epithelial tissue and memory B lymphocytes. The latently infected memory B cells are considered as a reservoir that makes the EBV evade immune through the transcription of a group of viral genes and the expression of certain

proteins. Most EBV infections are asymptomatic and can be developed to cause acute infectious mononucleosis. In addition, EBV is associated with epithelial and lymphoid malignancy (Renzette et al., 2014). Many studies show that EBV is considered an oncogenic virus that associated with many types of carcinoma including nasopharyngeal carcinoma (NPC), Burkett's lymphoma (BL), gastric carcinoma (GC), Hodgkin's lymphoma (HL) and Non-Hodgkin's lymphoma (Teow and Peh, 2017). Breast, prostate, and cervical cancers are also considered as EBV-associated cancers (Ahmad et al., 2023; Ali et al., 2025; Khalaf et al., 2024). Figure (1) shows the association of EBV with many types of cancer in a pyramid form and the percentage of each one (Teow and Peh, 2017).

EBV Latency and Oncogenicity

Analyzing the genetic variety of EBV in both healthy and diseased hosts throughout time, may shed light on the virus's transforming abilities. It might make it possible to create better treatments for cancers linked to EBV (Ahmed et al., 2025b; Mussa et al., 2022). Different EBV-mediated pathogenic pathways may be suggested by the varied EBV gene expression patterns seen in the various types of cancer. EBV has an outer envelope, various glycoproteins (GP) are embedded in the envelope, a nucleocapsid an icosahedral protein that wraps the DNA and a protein tegument. Many proteins are produced through the life cycle of EBV, some of them are structural and some are non-structural. The most abundant structural protein is GP 350/220. The genetic material of EBV has 172 kb, 0.5 kb is repetitive sequences in the terminal of viral DNA, and 3 kb repeated in the internal of the DNA (Hutt-Fletcher, 2015). Previous research has mostly used investigations of EBV nuclear antigen (EBNA) protein length variants (referred to as "EBNotype") to assess the genetic variety of distinct EBV genes in tumor tissues, peripheral blood, and oropharyngeal secretions. This data shows that there is diversity in six genes overall. Expression of EBV latency proteins EBV nuclear antigen 1 (EBNA 1), EBNA 2, EBNA 3A, EBNA 3B, EBNA 3C, and latent membrane proteins LMP 1, 2A, 2B can induce alteration on B lymphocyte proliferation causing permanent transformation (Renzette et al., 2014).

The EBV is classified into type A and type B with considerable sequence variation in the EBNA3A-C (BERF1-3) and EBNA2 (BYRF1) genes with small "sub-strain" differences in the genes Zebra (BZLF1), EBNA1 (BKRF1), LMP1 (BNLF1), and several additional. Prior studies revealed that the type A virus predominates in the majority of EBV-associated disorders and that it transforms B cells more effectively in vitro (Nanbo et al., 2018). There are more than 100 open reading frames (ORFs) in the EBV genome. These are named after the portion of the BamHI restriction in which they are situated (Ba abdullah et al., 2017). EBV gene expression is relatively restricted in most EBV-developing syndromes and is not associated with lytic genome replication or the generation of new virus particles. The latent episomal (closed circular) form of the virus genome is presented in each tumor cell in EBV-associated cancers, and host DNA polymerase replicates the viral genome along with host chromosomes during each cell division. The identification of latent episomal EBV- DNA is considered as evidence for the early role of EBV in developing tumors (Farrell, 2019).

In most EBV-associated malignancies linked to EBV latency. During the latent state, the virus, remains transcriptional active. The gene product is called the latent gene, the immediate early gene (IE) expressed independently, encodes for transcription proteins that are important for switch-on the lytic phase genes. Another group of genes named early gene where their effect occurs on the nucleotide metabolism and DNA synthesis of the host cell, Genes that include the most structural and non-structural proteins like IL-10 (BCRF1) are late gene switch-off by inhibition of lytic viral DNA synthesis (Zeng et al., 2024).

The latent genes play an important role in EBV-associated syndrome in a different way. Once the EBV infects the B lymphocyte it binds to CD 21 (CR2) and enters the cell membrane to deliver its genetic material to the host cell. The virus enters the latent phase and doesn't replicate (cell lysis) immediately. Subsequently, the expression of the latent gene will be initiated starting with EBNA2, and EBNA-LP leading to the expression of LMP1 whereas, the last expression in this process is EBNA1 which allows the viral genome to replicate. LMP 1 is known to possess carcinogenic properties based on the capacity to convert a rodent fibroblast and alter the phenotypic of B cells and epithelial cells (Overkamp et al., 2022). EBV-encoded RNAs (EBER 1 and 2) which are small non-polyadenylated RNAs with 10^5 to 10^7 copies per cell. They are thought to play a role in splicing for primary EBNA1 and LMP1, downregulation of apoptosis, suppressing interferon alpha and gamma, and enhancing IL-10 production. LMP1 is considered the most oncogenic EBV protein. It can cause upregulation of A-20 and BCL-2 genes (anti-apoptosis genes) that inhibit the apoptosis process in B cells (Kerr,

2020). Furthermore, it can cause upregulation for IL- 10 that inhibits immune response. LMP1 interacts with cellular protein tumor necrosis factor receptors (TNFR) that mediate cytoplasmic signaling causing stimulation of B cell and epithelial cell proliferation, thus, mediating the NF-kB signal transduction pathway. This leads to morphological changes and enhances the production of CD23, CD39, CD40, CD44, and MHC II which is a B cell activation marker. In addition, cellular adhesion molecules LFA-1 and ICAM-1 are overexpressed. It also enhances the activation of the JAK2-STAT pathway. The C terminal of LMP1 is responsible for the effects mentioned above (Quintanilla-Martinez et al., 2023).

EBV EBNA Protein

Four distinct promoters can be used to generate transcripts encoding the EBV nuclear antigen (EBNA). Transcription begins in BamHI-W (Wp) during the early phases of primary infection. After host cell transformation is confirmed, the promoter in BamHI-C (Cp) is switched on the lengthy (about 50–70 kb) primary transcripts from these two promoters include coding sequences for both EBNA1 and the additional EBNAs. Cp and Wp are silenced by methylation in latency types I and II, where EBNA1 is the only EBNA expressed, and transcription is started from a promoter in BamHI-Q (Qp). Qp is thought to be the real latent promoter for EBNA1 transcription, and it is controlled by EBNA1 autoregulation in a cell cycle-dependent way in addition via regulation mediated by cytokines, the fourth promoter is activated following lytic cycle entry that is localized in BamHI-F (Fp). Different levels of EBNA1 transcripts are produced by each of these unique EBNA1 promoters based on the kind of host cell and its activation state (Frontzek et al., 2023).

Nuclear protein EBNA1 is composed of a basic amino terminus, a variable length Gly/Ala repeat segment, a lengthy hydrophobic C-terminal domain with DNA-binding and dimerization activity, and another short basic domain with a nuclear localization sequence (Kimura et al., 2022). The EBNA1 C-terminal dimer domain's crystal structure was determined, and when it was attached to its corresponding DNA sequence, it revealed an unexpectedly strong structure. A partial palindrome sequence [TAGGATAGCATA-TGCTACCCAGATCCAG] that is presented at three locations in the EBV genome interacts with EBNA1 dimers to form DNA bonds. Two high-affinity sites exist a combination of two sequences in dyad symmetry (DS) two in tandem repeats of the cognate sequence (FR), and 20 tandem repeats in FR. A 1 kb intervening segment separates the FR and DS components. These come together to generate oriP, the plasmid replication origin. The 1 kb stretch between FR and DS loops out when EBNA1 binds to these locations, allowing the episome to replicate and remain in cycling cells (Nishimura et al., 2017).

EBNA1 is connected to host-cell chromosomes during mitosis, which is crucial for the segregation of episomes into progeny nuclei. The latency I promoter in BamHI Q lies downstream of the third EBNA1 binding site. EBNA1 binding to this location suppresses Qp activity, but E2F can overcome this inhibition, which means that Qp activity is cell-cycle dependent (Verhoeven et al., 2018). EBNA1 enhances transcription from cellular and EBV promoters, linking distant DNA sequences and binding to host-cell nucleosomes transcription and splicing factors like P32/Tap and EBp2. Moreover, it is believed that genetic instability results from EBNA1's capability to express the recombinase-activating genes RAG-1.

In addition, EBNA1 has an inhibitory effect, despite being an alien protein to the host is not destroyed by cytotoxic T lymphocytes, this results from the Gly/Ala repeat of the protein which stops endogenous MHC class I-restricted presentation. In the majority of healthy virus carriers, CD4/T-cells and antibodies reactive with EBNA1 are easily found. The latter is most likely the result of dendritic cells laden with EBNA1 obtained from the digestion of EBV-positive apoptotic cells (Zhang et al., 2022). There is a genetic diversity of EBNA2 proteins among type 1 EBV and type 2 that affect their ability to transform activity. While EBNA2 is important for the initial transformation growth, the initial EBV protein produced following the viral genome's transport to the nucleus is the EBNA2 protein. The transcription of EBNA2 is begun from Wp and Cp (Verhoeven et al., 2018). In vitro, it activates many genes specifically CD23, CD21, and the viral LMP1, and LMP2 genes. EBV in B-cell in vitro, the expression rate is limited in EBV-associated malignant tumors and nearly absent.

LMP1 EBV Protein

A highly abundant viral transcript in most latently infected B-cell lines is LMP1 mRNA, which originates from the BNLF1 open reading frame. Three exons are encoding the LMP1 protein which is an integral membrane protein with six short hydrophobic membrane- spanning a-helices connected by three short reverse turns that

are expected to loop out on the extracellular side of the membrane in front of its hydrophilic (small) and large (C) termini in the cytoplasm (Huang et al., 2024).

EBV-infected cells may produce a portion of LMP1 as MHC-II-containing secretory vesicles known as exosomes. Over half of LMP1 is found within cells, and its expression varies greatly even in clonal EBV/Bell populations from one cell to another. The degree of LMP1 expression varies significantly amongst various EBV-infected cell lines in vitro, similar to EBV-infected malignant cells in vivo. A poor prognosis has been associated with high expression levels of LMP1 in vivo (Müller Coan et al., 2022). LMP1 has a transforming ability. In addition to the oncogenic ability mentioned above, LMP1 lowers the CD40-CD40 ligand (He et al., 2024a). Only after the formation of the circular viral episome, the LMP2A, B mRNA is translated. Their distinct promoters produce distinct initial exons, and LMP2B lacks the majority of its N-terminal domain; the remaining exons are typical of LMP2A and B. Research with transgenic mice carrying the LMP2A gene has demonstrated that LMP2A, which is not carcinogenic in those mice, can give B-cells a signal for survival even in the absence of B-cell receptor expression (Wang and Ning, 2021). Some researchers are demonstrating the well-regulated co-expression of LMP1 and LMP2, along with EBNA1, in circulating EBV-carrying memory B-cells passing through tonsil lymphoid follicles in vivo lends additional support to this (Lo et al., 2021).

Nasopharyngeal Cancer

Types of NPC

As previously mentioned, NPC is an abrasive rare tumor in the retroperitoneal cavity. This type of cancer might exhibit three differentiation levels depending on histopathological features. According to the World Health Organization (WHO), the first type is a keratinizing squamous cell carcinoma (SCC) type I, Type II is nonkeratinizing carcinoma, and Type III is undifferentiated carcinoma also called lymphoepithelioma which has lymphoplasmacytic Infiltrate. This is the common type found in the endemic region with 97 % of all cases in southern China, whereas type II has around 75% of all cases found in Western countries. In addition to variations in histological characteristics, latent EBV infection is specific to nearly all NPC from endemic locations but absent in type I in non-endemic regions (Ahmed et al., 2022).

NPC Etiology

The Southern Chinese NPC's ethnic clustering implies that both environmental factors and genetic vulnerability played a role in the etiology of the disease, in addition to many studies show that the viral factor has a strong correlation with NPC (Ahmed et al., 2022).

Genetic factor

The majority of research done on Chinese people revealed that those who had HLA- A2 are more susceptible to NPC (Tsao et al., 2017). Other studies occur in the Chinese NPC family tree using highly polymorphic microsatellite markers revealed two susceptibility loci on chromosomes 4p15.1-q12 and 3p21, respectively, but not on the MHC region (Wong et al., 2021b). Another gene linked to an elevated risk of NPC was glutathione S-Transferase M1 (GSTM1), which functions as a detoxifier and repairs DNA (XRCC1 and hOGG1) (Su et al., 2024).

Environmental factors

The volatile Nitrosamine is considered as a causative agent for developing NPC. This compound is found in traditional southern Chinese food, specifically, salty fish and other preserved food (Li et al., 2015) . The increased consumption of these foods increases the risk of getting NPC, which is found among children in South China. In Hong Kong, the incidence of NPC was decreased in around 30% according to the changes in the traditional lifestyle especially, the lower intake of salty fish. Other environmental factors may increase the risk of NPC like smoking and exposure to formaldehyde (Sun et al., 2012).

EBV

There is a strong association between NPC and EBV since NPC patients have a high EBV antibody titer, particularly, in the IgA class. Most NPC patients have cancer cells that show latent EBV infection in endemic

areas. These findings suggest that viral latent infection may have occurred before the cancerous cell clone's growth. According to contemporary theory, EBV is essential for the development of invasive malignancies from nasopharyngeal epithelial cells (Kerr, 2019).

Signs, Symptoms, Diagnosis and Treatment of NPC

As initially stated, NPC occurs in the Rosenmüller's fossa, and many clinical features may be connected to NPC. Mass in the neck region, bloody sputum, obstruction in the nasal cavity, and others like tinnitus, neurological features like recurrent headache, and loss of hearing may be related to NPC. NPC can easily metastasize according to many lymphatic vessels in this region so cervical lymphadenopathy the most common manifestation, occurs.

Two systems are still used for diagnosing and prognosis of this disease: the Ho and the UICC/AJCC systems. They use CT (computed tomography) and MRI (magnetic resonance imaging) to know if the skull or brain is involved. The main treatment used for NPC is radiotherapy since the NPC is radiosensitive (Ahmed et al., 2025a; Al-Mhanna et al., 2022).

The Role of Oncogenicity of EBV in NPC

Compared to other cancers of the head and neck, NPC is one of the EBV-associated malignancies with a significant potential for metastatic spread. This is indicated by the existence of the infiltration of immune cells surrounding tumor regions and the predominance of EBV infection. On the other hand, cancer cells may eventually avoid immune clearance from the host and continue to proliferate, indicating the presence of an immunosuppressive milieu that renders these immune cells depleted and anergic (Chang et al., 2021). PD-L1 are known to be significant immunosuppressive factor. It was just demonstrated that certain EBV-associated cancers, such as NPC, had elevated levels of PD-L1 (Yuan et al., 2022). Nevertheless, little is known about the underlying mechanism of PD-L1 regulation and its clinical implications in NPC linked with EBV. Many studies show the correlation between elevated PD-L1 and types of cancer that are associated with EBV such as lymphoma (Zhang et al., 2018) , hepatocellular cancer , squamous cell cancer and NPC (Feng et al., 2002). Helicobacter pylori were also found to cause elevation of expression of PD-L1 in gastric cancer (Machlowska et al., 2020).

The down-regulation of pSTAT3 was accompanied by a clear dose-response pattern in the amount of PD-L1 after phosphorylated JAK3 was inhibited. This suggests that the JAK3- STAT3 pathway is essential for altering the expression of PD-L1 by LMP1. Figure 3 shows the mechanisms of elevated PD-L1 in NPC-positive EBV (Fang et al., 2014). Many studies found that many inflammatory factors are elevated through the immune response against tumors or viruses which may be used by the cancer cell to evade immune surveillance of all the inflammatory agents, IFN-γ was the most well-known for its ability to modify the expression of PD-L1 (Yi et al., 2021). By starting the production of the transcriptional factor interferon regulatory factor-1 (IRF-1), IFN-γ can control PD-L1 at the transcriptional level. This factor binds to the PD-L1 promoter through two locations via the JAK/STAT pathway (Gou et al., 2020).

NPC and EBV

NPC with EBV infections shows elevated PD-L1 levels at least due to LMP1-mediated oncogenicity and immunological regulation via IFN-γ excretion. A PD-L1 in low levels is linked with improved local disease control (Lee et al., 2024). NPC type III is strongly associated with EBV. EBV was found in almost all samples collected from low-incidence to high-incidence NPC by using various techniques like PCR and immunohistochemistry staining. The LMP1 shows oncogenic features that were expressed in 78% of NPC samples (Yamaguchi et al., 2022). Many mutations occur in the C terminus region of LMP 1 converting it from a non-oncogenic to oncogenic protein (Iaccarino et al., 2021). The most important one is 30bp deletion. Another mutation that was identified in the LMP1 gene includes a point mutation resulting of the loss of a restriction site called Xhol (Lobrano et al., 2023). Hui Shien studied these mutations and their correlation with NPC in Malaysia using PCR and found that the incidence rate of 30-bp deletion mutation was lower compared to the previous studies, the loss of Xhol resection site in NPC was the same incidence of previous study occurred in the endemic region like southern China that means the association of 30-bp deletion and loss of

XhoI restriction site with type III NPC need further investigation (He et al., 2024b).

Many studies of the LMP 1 gene among NPC in China, which is considered a high incidence rate region showed a high frequency of XhoI loss in exon 1 and a 30bp deletion in exon 3 (Ying et al., 2021). Blake *et al* found that the 30bp deletion LMP 1 has a longer half- life than the LMP1 in prototype EBV and has a higher ability to activate many pathways like NF-KB.9 (Vranic et al., 2021). Another study of the LMP1 variant occurring in EBV-associated NPC among Tunisian patients found a rare LMP1 variant 69bp deletion in the C terminus region covering the 30bp deletion in two NPC samples., The study found that these deletions are 71.4% frequent in NPC patients suggesting that these variants could be associated with NPC among the Tunisian population (Ahmad et al., 2016). Unfortunately, 70% of NPC patients are diagnosed in advanced stages. Taking into consideration that the NPC has a high metastatic rate, advanced-stage cases have a three-year survival rate lower than the patients that are diagnosed at stage 1 or stage 2. Thus, the improvement of the early diagnosis of NPC can reduce its mortality rate. The aim of this study is to employ 30-bp deletion LMP1 as a biomarker to help clinicians diagnose NPC early, improving prognosis and reducing mortality rates (Ahmed et al., 2022).

Conclusion

This review solidifies the critical role of the EBV's LMP1 30-bp deletion as a pivotal oncogenic driver in NPC. The consistent association of this specific genetic variant with enhanced tumor aggressiveness, metastatic potential, and poorer patient outcomes firmly establishes its utility as a robust prognostic biomarker. Its high prevalence in NPC tumors further underscores its potential for improving molecular diagnosis and risk stratification. Ultimately, detecting this deletion is a crucial step toward precision oncology, promising to guide personalized treatment strategies and paving the way for novel therapies targeting its unique pathogenic mechanisms.

Funding: This literature review received no external funding.

Institutional Review Board Statement: Not applicable.

Acknowledgments: The authors would like to thank Zarqa University, Amman, Jordan for providing the facilities to conduct this informative literature review.

Conflicts of Interest: The authors declare no conflict of interest.

REFERENCES

Ahmad, S., L. Lambuk, N. Ahmed, A. Mussa, V. Tee, R.A. Mohd Idris, N.F. Sahran, Y.Y. Chan, R. Hassan, and Y.Y. Lee. 2023. Efficacy and safety of nab-paclitaxel in metastatic gastric cancer: a meta-analysis. *Nanomedicine*. 18:1733-1744.

Ahmad, S.M., T.H. Borch, M. Hansen, and M.H. Andersen. 2016. PD-L1-specific T cells. *Cancer immunology, immunotherapy : CII*. 65:797-804.

Ahmed, N., M.A.H.A. Abusalah, M. Absar, M.H. Nasir, A. Farzand, I. Ahmad, Z. Sohail, K.K.B. Singh, A.A. Baig, and C.Y. Yean. 2025a. The Microbial Sources of Bioactive Compounds: Potential Anticancer Therapeutic Options. *Nano Life*. 15:2430007.

Ahmed, N., M.A.H.A. Abusalah, M. Absar, M.S. Noor, B. Bukhari, S.A. Anjum, K.K.B. Singh, and C.Y. Yean. 2025b. Carbon-based Nanomaterials as Multifunctional Particles for Cancer Diagnosis and Treatment. *Nano Life*. 15:2430005.

Ahmed, N., M.A.H.A. Abusalah, A. Farzand, M. Absar, N.Y. Yusof, A.A. Rabaan, H. AlSaihati, A. Alshengeti, S. Alwarthan, and H.S. Alsuwailem. 2022. Updates on Epstein–Barr Virus (EBV)-Associated Nasopharyngeal Carcinoma: Emphasis on the Latent Gene Products of EBV. *Medicina*. 59:2.

Ahmed, N., A.A. Rabaan, A.S. Alwashmi, H. Albayat, M.M. Mashraqi, A.A. Alshehri, M. Garout, W.A. Abduljabbar, N.Y. Yusof, and C.Y. Yean. 2023. Immunoinformatic Execution and Design of an Anti-Epstein–Barr Virus Vaccine with Multiple Epitopes Triggering Innate and Adaptive Immune Responses. *Microorganisms*. 11:2448.

Al-Mhanna, S.B., W.S.W. Ghazali, M. Mohamed, A.A. Rabaan, E.Y. Santali, J.H. Alestad, E.Y. Santali, S. Arshad, N. Ahmed, and H.A. Afolabi. 2022. Effectiveness of physical activity on immunity markers and quality of life in cancer patient: a systematic review. *PeerJ*. 10:e13664.

Ali, A., M. Alghamdi, S.S. Marzuki, T.A.D.A.A. Tengku Din, M.S. Yamin, M. Alrashidi, I.S. Alkhazi, and N. Ahmed. 2025. Exploring AI Approaches for Breast Cancer Detection and Diagnosis: A Review Article. *Breast Cancer: Targets and Therapy*:927-947.

Ba abdullah, M.M., R.D. Palermo, A.L. Palser, N.E. Grayson, P. Kellam, S. Correia, A. Szymula, and R.E. White. 2017.

Heterogeneity of the Epstein-Barr virus (EBV) major internal repeat reveals evolutionary mechanisms of EBV and a functional defect in the prototype EBV strain B95-8. *Journal of virology*. 91:10.1128/jvi. 00920-00917.

Banko, A.V., I.B. Lazarevic, M.M. Folic, V.B. Djukic, A.M. Cirkovic, D.Z. Karalic, M.D. Cupic, and T.P. Jovanovic. 2016. Characterization of the variability of Epstein-Barr virus genes in nasopharyngeal biopsies: Potential predictors for carcinoma progression. *PloS one*. 11:e0153498.

Chang, E.T., W. Ye, Y.X. Zeng, and H.O. Adami. 2021. The Evolving Epidemiology of Nasopharyngeal Carcinoma. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology*. 30:1035-1047.

da Costa, V.G., A.C. Marques-Silva, and M.L. Moreli. 2015. The Epstein-Barr virus latent membrane protein-1 (LMP1) 30-bp deletion and XhoI-polymorphism in nasopharyngeal carcinoma: a meta-analysis of observational studies. *Systematic reviews*. 4:46.

Fang, W., J. Zhang, S. Hong, J. Zhan, N. Chen, T. Qin, Y. Tang, Y. Zhang, S. Kang, and T. Zhou. 2014. EBV-driven LMP1 and IFN-γ up-regulate PD-L1 in nasopharyngeal carcinoma: Implications for oncotargeted therapy. *Oncotarget*. 5:12189.

Farrell, P.J. 2019. Epstein–Barr virus and cancer. *Annual Review of Pathology: Mechanisms of Disease*. 14:29-53.

Feng, B.-J., W. Huang, Y.Y. Shugart, M.K. Lee, F. Zhang, J.-C. Xia, H.-Y. Wang, T.-B. Huang, S.-W. Jian, and P. Huang. 2002. Genome-wide scan for familial nasopharyngeal carcinoma reveals evidence of linkage to chromosome 4. *Nature genetics*. 31:395-399.

Frontzek, F., A.M. Staiger, R. Wullenkord, M. Grau, M. Zapukhlyak, K.S. Kurz, H. Horn, T. Erdmann, F. Fend, J. Richter, W. Klapper, P. Lenz, S. Hailfinger, A. Tasidou, M. Trautmann, W. Hartmann, A. Rosenwald, L. Quintanilla-Martinez, G. Ott, I. Anagnostopoulos, and G. Lenz. 2023. Molecular profiling of EBV associated diffuse large B-cell lymphoma. *Leukemia*. 37:670-679.

Gou, Q., C. Dong, H. Xu, B. Khan, J. Jin, Q. Liu, J. Shi, and Y. Hou. 2020. PD-L1 degradation pathway and immunotherapy for cancer. *Cell death & disease*. 11:955.

Guo, R., Y.-P. Mao, L.-L. Tang, L. Chen, Y. Sun, and J. Ma. 2019. The evolution of nasopharyngeal carcinoma staging. *The British journal of radiology*. 92:20190244.

He, F., Y. Gong, G. Tao, J. Zhang, Q. Wu, Y. Tan, Y. Cheng, C. Wang, J. Yang, L. Han, Z. Wang, Y. Gao, J. He, R. Bai, P. Sun, X. Yu, Y. Zhou, and C. Xie. 2024a. Targeting the LMP1-ALIX axis in EBV(+) nasopharyngeal carcinoma inhibits immunosuppressive small extracellular vesicle secretion and boosts anti-tumor immunity. *Cancer communications (London, England)*. 44:1391-1413.

He, Y., M. Zhu, X. Lai, H. Zhang, and W. Jiang. 2024b. The roles of PD-L1 in the various stages of tumor metastasis. *Cancer metastasis reviews*. 43:1475-1488.

Huang, J., X. Zhang, X. Nie, X. Zhang, Y. Wang, L. Huang, X. Geng, D. Li, L. Zhang, G. Gao, and P. Gao. 2024. Assembly and activation of EBV latent membrane protein 1. *Cell*. 187:4996-5009.e4914.

Hutt-Fletcher, L.M. 2015. EBV glycoproteins: where are we now? *Future virology*. 10:1155-1162.

Iaccarino, A., M. Salatiello, I. Migliatico, C. De Luca, G. Gragnano, M. Russo, C. Bellevicine, U. Malapelle, G. Troncone, and E. Vigliar. 2021. PD-L1 and beyond: Immuno-oncology in cytopathology. *Cytopathology : official journal of the British Society for Clinical Cytology*. 32:596-603.

Kerr, J. 2020. Early Growth Response Gene Upregulation in Epstein-Barr Virus (EBV)-Associated Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). *Biomolecules*. 10.

Kerr, J.R. 2019. Epstein-Barr virus (EBV) reactivation and therapeutic inhibitors. *Journal of clinical pathology*. 72:651-658.

Khalaf, T.K., N. Ismail, N.A. Nazri, N. Ahmed, A.I. Yajid, R. Mohamud, and R. Kadir. 2024. Pereskia bleo augments NK cell cytotoxicity against triple-negative breast cancer cells (MDA-MB-231). *PeerJ*. 12:e18420.

Kimura, H., L. de Leval, Q. Cai, and W.S. Kim. 2022. EBV-associated NK and T-cell lymphoid neoplasms. *Current opinion in oncology*. 34:422-431.

Lao, T.D., D.H. Nguyen, T.M. Nguyen, and T.A.H. Le. 2017. Molecular screening for Epstein-Barr virus (EBV): detection of genomic EBNA-1, EBNA-2, LMP-1, LMP-2 among Vietnamese patients with nasopharyngeal brush samples. *Asian Pacific Journal of Cancer Prevention: APJCP*. 18:1675.

Lee, D., M. Cho, E. Kim, Y. Seo, and J.H. Cha. 2024. PD-L1: From cancer immunotherapy to therapeutic implications in multiple disorders. *Molecular therapy : the journal of the American Society of Gene Therapy*. 32:4235-4255.

Li, Y., W. Wan, T. Li, J. Cao, and G. Xu. 2015. GSTM1 null genotype may be associated with an increased nasopharyngeal cancer risk in South China: an updated meta-analysis and review. *OncoTargets and therapy*. 8:2479-2484.

Lo, A.K., C.W. Dawson, H.L. Lung, K.L. Wong, and L.S. Young. 2021. The Role of EBV-Encoded LMP1 in the NPC Tumor Microenvironment: From Function to Therapy. *Front Oncol*. 11:640207.

Lobrano, R., P. Paliogiannis, A. Zinellu, G. Palmieri, I. Persico, A.A. Mangoni, and A. Cossu. 2023. PD-L1 Expression in Cutaneous Angiosarcomas: A Systematic Review with Meta-Analysis. *Current oncology (Toronto, Ont.)*. 30:5135-5144.

Machlowska, J., J. Baj, M. Sitarz, R. Maciejewski, and R. Sitarz. 2020. Gastric Cancer: Epidemiology, Risk Factors,

Classification, Genomic Characteristics and Treatment Strategies. *International journal of molecular sciences*. 21.

Müller Coan, B.G., E. Cesarman, M.L. Acencio, and D. Elgui de Oliveira. 2022. Latent Membrane Protein 1 (LMP1) from Epstein-Barr Virus (EBV) Strains M81 and B95.8 Modulate miRNA Expression When Expressed in Immortalized Human Nasopharyngeal Cells. *Genes*. 13.

Mussa, A., R.A. Mohd Idris, N. Ahmed, S. Ahmad, A.H. Murtadha, T.A.D.A.A. Tengku Din, C.Y. Yean, W.F. Wan Abdul Rahman, N. Mat Lazim, and V. Uskoković. 2022. High-dose vitamin C for cancer therapy. *Pharmaceuticals*. 15:711.

Nanbo, A., T. Noda, and Y. Ohba. 2018. Epstein–Barr virus acquires its final envelope on intracellular compartments with golgi markers. *Frontiers in microbiology*. 9:454.

Nishimura, M., J. Wang, A. Wakata, K. Sakamoto, and Y. Mori. 2017. Crystal Structure of the DNA-Binding Domain of Human Herpesvirus 6A Immediate Early Protein 2. *J Virol*. 91.

Overkamp, M., L. Quintanilla-Martinez, and F. Fend. 2022. [EBV-associated lymphoproliferative disorders]. *Pathologie (Heidelberg, Germany)*. 43:282-291.

Quintanilla-Martinez, L., S.H. Swerdlow, T. Tousseyn, C. Barrionuevo, S. Nakamura, and E.S. Jaffe. 2023. New concepts in EBV-associated B, T, and NK cell lymphoproliferative disorders. *Virchows Archiv : an international journal of pathology*. 482:227-244.

Renzette, N., M. Somasundaran, F. Brewster, J. Coderre, E.R. Weiss, M. McManus, T. Greenough, B. Tabak, M. Garber, and T.F. Kowalik. 2014. Epstein-Barr virus latent membrane protein 1 genetic variability in peripheral blood B cells and oropharyngeal fluids. *Journal of Virology*. 88:3744-3755.

Su, Z.Y., P.Y. Siak, Y.Y. Lwin, and S.C. Cheah. 2024. Epidemiology of nasopharyngeal carcinoma: current insights and future outlook. *Cancer metastasis reviews*. 43:919-939.

Sun, Z.F., J. Zhang, H.M. Xu, G.L. Wang, and P. Dong. 2012. Association between GSTM1 polymorphism and nasopharyngeal cancer susceptibility: a meta-analysis. *Asian Pacific journal of cancer prevention : APJCP*. 13:5817-5821.

Teow, S.-Y., and S.-C. Peh. 2017. Exosomes as the promising biomarker for Epstein-Barr virus (EBV)-associated cancers. *Novel Implications of Exosomes in Diagnosis And Treatment of Cancer And Infectious Diseases*.

Tsao, S.W., C.M. Tsang, and K.W. Lo. 2017. Epstein-Barr virus infection and nasopharyngeal carcinoma. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*. 372.

Verhoeven, R.J., S. Tong, J. Zong, Y. Chen, S.-W. Tsao, J. Pan, and H. Chen. 2018. NF-κB Signaling Regulates Epstein–Barr Virus Bam HI-Q-Driven EBNA1 Expression. *Cancers*. 10:119.

Vranic, S., F.S. Cyprian, Z. Gatalica, and J. Palazzo. 2021. PD-L1 status in breast cancer: Current view and perspectives. *Seminars in cancer biology*. 72:146-154.

Wang, L., and S. Ning. 2021. New Look of EBV LMP1 Signaling Landscape. *Cancers (Basel)*. 13.

Wong, K.C., E.P. Hui, K.-W. Lo, W.K.J. Lam, D. Johnson, L. Li, Q. Tao, K.C.A. Chan, K.-F. To, and A.D. King. 2021a. Nasopharyngeal carcinoma: an evolving paradigm. *Nature reviews Clinical oncology*. 18:679-695.

Wong, K.C.W., E.P. Hui, K.W. Lo, W.K.J. Lam, D. Johnson, L. Li, Q. Tao, K.C.A. Chan, K.F. To, A.D. King, B.B.Y. Ma, and A.T.C. Chan. 2021b. Nasopharyngeal carcinoma: an evolving paradigm. *Nature reviews. Clinical oncology*. 18:679-695.

Yamaguchi, H., J.M. Hsu, W.H. Yang, and M.C. Hung. 2022. Mechanisms regulating PD-L1 expression in cancers and associated opportunities for novel small-molecule therapeutics. *Nature reviews. Clinical oncology*. 19:287-305.

Yi, M., M. Niu, L. Xu, S. Luo, and K. Wu. 2021. Regulation of PD-L1 expression in the tumor microenvironment. *Journal of hematology & oncology*. 14:10.

Ying, H., X. Zhang, Y. Duan, M. Lao, J. Xu, H. Yang, T. Liang, and X. Bai. 2021. Non-cytomembrane PD-L1: An atypical target for cancer. *Pharmacological research*. 170:105741.

Yuan, L., S. Li, Q. Chen, T. Xia, D. Luo, L. Li, S. Liu, S. Guo, L. Liu, C. Du, G. Jia, X. Li, Z. Lu, Z. Yang, H. Liu, H. Mai, and L. Tang. 2022. EBV infection-induced GPX4 promotes chemoresistance and tumor progression in nasopharyngeal carcinoma. *Cell death and differentiation*. 29:1513-1527.

Zeng, C., M. Qiao, Y. Chen, and H. Xie. 2024. EBV-positive glycoproteins associated with nasopharyngeal carcinoma. *Pathology, research and practice*. 260:155427.

Zhang, J., T. Huang, Y. Zhou, A.S.L. Cheng, J. Yu, K.F. To, and W. Kang. 2018. The oncogenic role of Epstein-Barr virus-encoded microRNAs in Epstein-Barr virus-associated gastric carcinoma. *Journal of cellular and molecular medicine*. 22:38-45.

Zhang, Z., X. Tang, J. Li, and Q. Yang. 2022. Analysis of the mechanism regulating the killing effect of EBNA1 on EBV-associated B-cell tumors. *Cellular and molecular biology (Noisy-le-Grand, France)*. 68:92-95.