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Polymorphisms in the *LMP1* gene in patients with gastric cancer associated with Epstein–Barr virus (*Orthoherpesviridae: Gammaherpesvirinae: Lymphocryptovirus: Lymphocryptovirus humangamma 4*)

Alexandra S. Vasilyeva^{1,2✉}, Alina A. Margusheva¹, Artem D. Molchanov^{1,3}, Artem A. Rtishchev², Bogdan S. Cherepovich², Valeria A. Domanskaya^{1,3}, Vladimir E. Gurtsevich¹, Ksenia V. Smirnova¹

¹N.N. Blokhin National Medical Research Center of Oncology, Ministry of Health of Russia, 115478, Moscow, Russia;

²I.I. Mechnikov Research Institute of Vaccines and Serums, 105064, Moscow, Russia;

³I.M. Sechenov First Moscow State Medical University (Sechenov University), Ministry of Health of Russia, 119991, Moscow, Russia

Abstract

Introduction. Epstein–Barr virus (EBV) is a widespread gamma-herpesvirus associated with a number of malignancies, including nasopharyngeal carcinoma and gastric cancer (GC/EBV+). The primary oncogenic protein of EBV is latent membrane protein 1 (LMP1). Genetic variability of the LMP1 protein affects its oncogenic activity and clinical manifestations.

Objective. To investigate the optimal threshold value for EBV viral load, determine the correlation between high viral load and the detection of the *LMP1* gene in the blood of patients with GC/EBV+, and to identify mutations in the C-terminal domains of the *LMP1* gene that may affect protein function.

Materials and methods. Total DNA was extracted from 227 blood samples of GC patients. The *LMP1* gene was amplified using nested PCR. EBV DNA viral load in blood samples was analyzed by qPCR, followed by receiver operating characteristic (ROC) analysis and interquartile range (IQR) assessment. A selection criterion for positive DNA samples (EBV+) was established based on the mean viral load and ROC threshold.

Results. ROC curve analysis and descriptive statistics identified 23 EBV-positive (EBV+) DNA samples, with the following results: AUC (area under the curve) = 0.83, optimal threshold 526.92 copies/reaction, sensitivity 0.69, specificity 0.87, and mean viral load: 513.5 copies/reaction. A statistically significant association was found between detection of the *LMP1* gene in the blood and viral load level (χ^2 test $p = 0.018$; Mann–Whitney U test $p < 0.0001$). Additionally, synonymous and nonsynonymous mutations were identified in regions of *LMP1* gene coding the C-terminal activating domains (CTAR1 and CTAR2).

Conclusion. The findings highlight the heterogeneous molecular nature of EBV-associated gastric cancer, including genetic mutations in the *LMP1* gene.

Keywords: Epstein–Barr virus; EBV-associated gastric cancer (GC/EBV+); *LMP1* (latent membrane protein 1); malignant tumors; polymerase chain reaction (PCR); sequence analysis

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Ethical approval. The study was conducted with the voluntary informed consent of patients. The study protocol was approved by the Ethics Committee of the N.N. Blokhin National Medical Research Center of Oncology of the Ministry of Health of Russia (Protocol No. 1126 dated April 18, 2023).

Полиморфизм гена *LMP1* у больных раком желудка, ассоциированным с вирусом Эпштейна–Барр (*Orthoherpesviridae: Gammaherpesvirinae: Lymphocryptovirus: Lymphocryptovirus humangamma 4*)

Васильева А.С.^{1,2✉}, Маргушева А.А.¹, Молчанов А.Д.^{1,3}, Ртищев А.А.², Черепович Б.С.², Доманская В.А.^{1,3}, Гурцевич В.Э.¹, Смирнова К.В.¹

¹ФГБУ «Национальный медицинский исследовательский центр онкологии им. Н.Н. Блохина» Минздрава России, 115478, г. Москва, Россия;

²ФГБНУ «Научно-исследовательский институт вакцин и сывороток им. И.И. Мечникова», 105064, г. Москва, Россия;

³ФГАОУ ВО «Первый Московский государственный медицинский университет им. И.М. Сеченова» Минздрава России (Сеченовский Университет), 119991, г. Москва, Россия

Резюме

Введение. Вирус Эпштейна–Барр (ВЭБ) – широко распространенный гамма-герпесвирус, ассоциированный с рядом злокачественных новообразований, включая рак носоглотки и рак желудка (РЖ/ВЭБ+). Основным онкогенным белком ВЭБ является латентный мембранный белок 1 (LMP1). Генетическая вариабельность белка LMP1 влияет на его онкогенную активность и клинические проявления.

Цель. Выяснить оптимальное пороговое значение вирусной нагрузки ВЭБ, определить наличие в образцах крови больных РЖ/ВЭБ+ корреляции между высокой вирусной нагрузкой и амплификацией гена *LMP1*, а также выявить наличие мутаций в С-терминальных доменах гена *LMP1*, способных изменять функции белка.

Материалы и методы. Исследовали тотальную ДНК, выделенную из 227 образцов крови больных раком желудка. Ген *LMP1* амплифицировали методом гнездовой полимеразной цепной реакции (ПЦР). Вирусную нагрузку ДНК ВЭБ в образцах крови анализировали методом количественной ПЦР с последующим проведением ROC-анализа (receiver operating characteristic) и расчета интерквартильного размаха (IQR), где на основе среднего значения вирусной нагрузки и ROC-порога был установлен критерий отбора положительных образцов ДНК ВЭБ (ВЭБ+).

Результаты. Анализ ROC-кривой и описательной статистики позволил выделить 23 ВЭБ+ образца ДНК на основании результатов: AUC (площадь под кривой) = 0,83, оптимального порога 526,92 копии/реакция, чувствительности 0,69, специфичности 0,87 и среднего значения вирусной нагрузки 513,5 копии/реакция. Выявлена статистически значимая связь между амплификацией гена *LMP1* в крови и уровнем вирусной нагрузки (критерий $\chi^2 p = 0,018$; U-критерий Манна–Уитни $p < 0,0001$). Кроме того, идентифицированы синонимичные и несинонимичные мутации в С-терминальных активизирующих доменах (STAR1 и STAR2) белка LMP1.

Заключение. Полученные результаты указывают на гетерогенную молекулярную природу РЖ/ВЭБ+, включая генетические мутации в *LMP1*.

Ключевые слова: вирус Эпштейна–Барр (ВЭБ); ВЭБ-ассоциированный рак желудка (РЖ/ВЭБ+); *LMP1* (латентный мембранный белок 1); злокачественные опухоли; полимеразная цепная реакция (ПЦР); сиквенсный анализ

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Introduction

Epstein-Barr virus (EBV) is one of the most common herpes viruses, infecting more than 90% of the adult population worldwide [1]. According to official information from the International Committee on Taxonomy of Viruses (ICTV), EBV belongs to the *Orthoherpesviridae* family, *Gammaherpesvirinae* subfamily, *Lymphocryptovirus* genus and *Lymphocryptovirus humangamma 4* species¹. According to the International Agency for Research on Cancer (IARC), EBV is included in the list of 11 oncogenic infections in humans and is classified as a Group I carcinogen with a direct oncogenic effect on the host organism [2].

After primary infection, the virus becomes latent, persisting in B lymphocytes and epithelial cells throughout the host's life. EBV is associated with the development of various malignant neoplasms, including tumors of epithelial origin, such as nasopharyngeal carcinoma and one of the subtypes of gastric cancer (GC) – EBV-associated gastric cancer (GC/EBV+) [3].

The key EBV oncogene involved in the transformation of infected cells is latent membrane protein 1 (LMP1). This viral oncoprotein functions as a constitutively active analog of the tumor necrosis factor receptor (TNFR), which contributes to the activation of various signaling cascades, such as NF- κ B, JNK, PI3K/Akt and STAT [4]. The activation of these signaling cascades creates favorable conditions for survival, proliferation, and suppression of apoptosis in infected cells, a process that is a key stage in carcinogenesis (**Fig. 1**).

The structure of LMP1 consists of a short cytoplasmic N-terminal end, six transmembrane domains, and a long cytoplasmic C-terminal end, which contains two well-studied activation domains: CTAR1, CTAR2 (C-terminal activation domains 1 and 2), and a third, less well-studied domain, CTAR3. The N-terminal domain is primarily responsible for LMP1 binding to the membrane and its oligomerization. CTAR domains perform most of the regulatory functions of LMP1 (**Fig. 1**) [5].

The classification of LMP1 variants is based on the polymorphism of the C-terminal activation region (CTAR), which interacts with the intracellular adapters TRAF and TRADD. LMP1 plays a key role in the development and progression of EBV-associated malignant tumors, making it a promising prognostic marker for patients with neoplasms such as nasopharyngeal carcinoma [6].

LMP1 variants differ in structure, expression level, signaling pathway activity, and clinical significance. Currently, several major LMP1 variants have been described: B95-8, China1/CAO, Med+, NC, as well as less common variants such as Alaskan, GD1, HKNPC1, and others [7, 8]. These variants differ in their geographical distribution, biological activity, and association with specific diseases.

Thus, the LMP1 China1/CAO variant, which has an increased ability to transform B lymphocytes *in vitro*,

activate NF- κ B, and initiate signaling cascades of multiple genes [9], is most often associated with the development of nasopharyngeal cancer in Asian populations. At the same time, the B95-8 variant, which is less effective at transforming B lymphocytes *in vitro*, is usually associated with lymphomas and infectious mononucleosis in Western countries [10].

Studying the variability of the LMP1 protein is of fundamental importance, since its heterogeneity and high level of polymorphism may be key factors determining the clinical picture of EBV-associated GC. Moreover, the molecular variant of LMP1 can be used as a marker of GC/EBV+, correlating with disease manifestations (remission, recurrence) and reflecting the effectiveness of the therapy.

The aim of the study was to determine the threshold value of EBV copy number in blood samples that allows distinguishing patients with high viral load, as well as to identify a number of significant mutations in the CTAR protein of LMP1 in patients with GC/EBV+, which could potentially influence the clinical picture and course of the disease, and to assess the relationship between high EBV viral load and the presence or absence of the *LMP1* gene sequences in the blood.

Materials and methods

Study material

Total DNA samples isolated from peripheral blood of 227 patients with newly diagnosed, morphologically confirmed GC who had not previously received anticancer therapy were studied. The material was obtained from patients from central regions of Russia undergoing treatment at the N.N. Blokhin National Medical Research Center for Oncology of the Russian Ministry of Health. The study was conducted with the voluntary informed consent of all patients. The study protocol was approved by the Ethics Committee of the N.N. Blokhin National Medical Research Center for Oncology (Protocol No. 1126 dated 04/18/2023).

DNA extraction

DNA was extracted from blood samples using the ExtractDNA Blood and Cells kit (Eurogen, Russia) according to the manufacturer's protocol. To control DNA quality, the A260/A280 optical density ratio was determined, which averaged 1.8, indicating high nucleic acid purity and suitability for further analysis. Samples with a concentration of at least 20 ng/ μ L dissolved in 50 μ L of elution buffer (Eurogen, Russia) were selected for the study.

Polymerase chain reaction with real-time detection of results

The number of copies of EBV DNA in the samples was determined using real-time polymerase chain reaction (qPCR) with minor modifications to previously published methodological recommendations [11, 12]. A ready-made PCR mixture, QuantiTect SYBR Green PCR Kit (Qiagen, Germany), and a standard set of primers (**Table 1**) were used for qPCR. qPCR was performed in accordance

¹ICTV (2025). Available on: <https://ictv.global/report/chapter/orthoherpesviridae/orthoherpesviridae/lymphocryptovirus> (дата доступа: 16.12.2025).

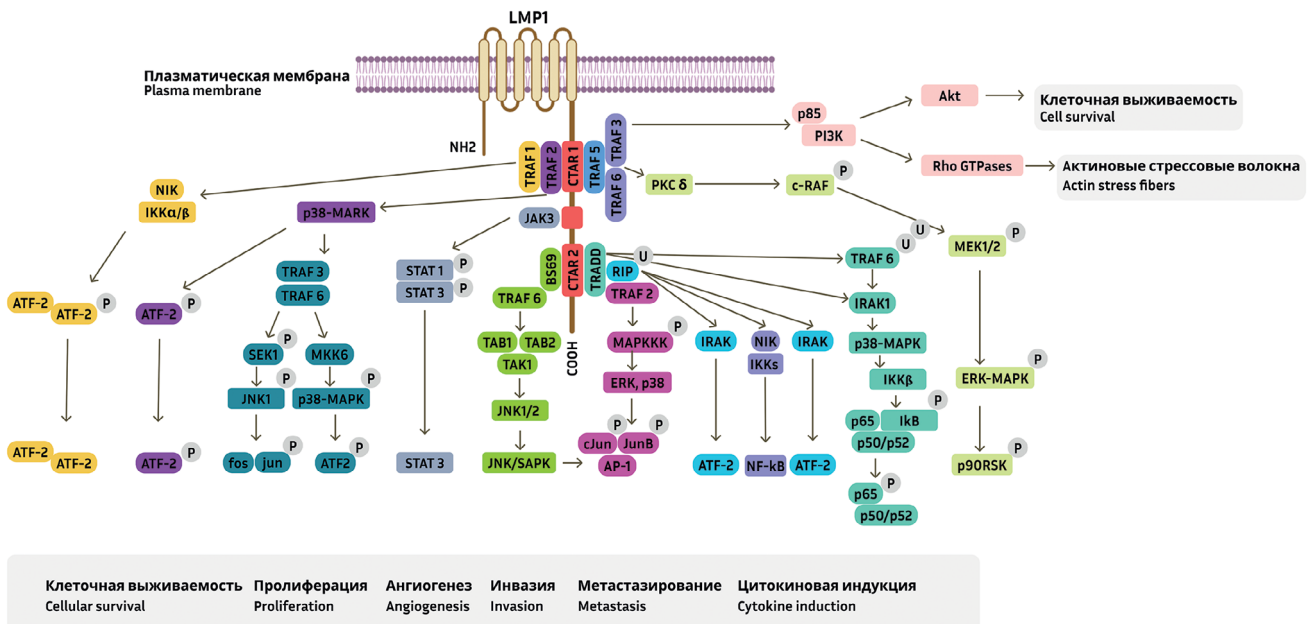


Fig. 1. LMP1-signaling pathways and associated cellular processes in EBV-associated malignancies.

Рис. 1. Сигнальные пути, опосредованные LMP1, и связанные с ними клеточные процессы при ВЭБ-ассоциированных злокачественных новообразованиях.

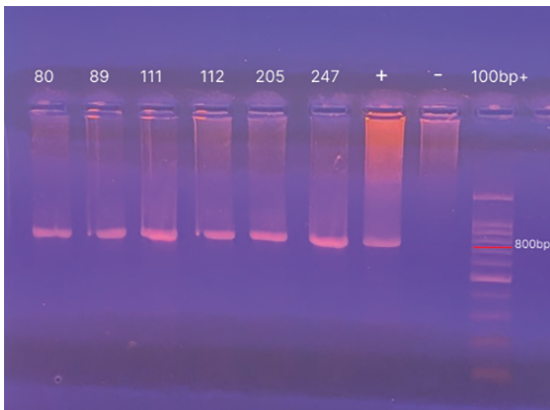


Fig. 2. Visualization of amplified *LMP1* gene DNA samples with the target length of 799 bp in 1.5% agarose gel using a 100 bp+ DNA ladder.

80, 89, 111, 112, 205, 247 – LMP1+/EBV+ samples; «+» – positive LMP1 control; «-» – negative control.

Рис. 2. Визуализация амплифицированных образцов ДНК гена *LMP1* искомой длины 799bp на 1,5% агарозном геле с использованием маркера длин 100bp+.

80, 89, 111, 112, 205, 247 – образцы LMP1+/ВЭБ+; «+» – положительный контроль на LMP1; «-» – отрицательный контроль.

Table 1. Nucleotide sequences of primers and probes used for real-time PCR

Таблица 1. Нуклеотидные последовательности праймеров и зонда, используемые при постановке ПЦП в реальном времени

Primer Праймер	Subsequence Последовательность
W-44F	ccc-aac-act-cca-cca-cac-c
W-119R	tct-tag-gag-ctg-tcc-gag-gg
W-67T	(FAM)ca-cac-act-aca-cac-acc-cac-ccg-tct-c(RTQ1)

with the manufacturer’s recommendations on a Real-time CFX 96 Maestro amplifier (Biorad, Germany). To construct a standard calibration curve and quantitatively determine the number of copies of EBV DNA, we used DNA isolated from the Namalwa cell line, in which 3.3 pg of genomic DNA contains one viral copy [13].

Amplification of the LMP1 gene by nested polymerase chain reaction

Nested PCR was performed to detect the *LMP1* gene in isolated blood samples in two stages using external and internal primers (Table 2) [14]. A ready-made PCR Screen mix 5x – HS reaction mixture (Eurogen, Russia) was used for PCR, and amplification was performed according to the manufacturer’s recommendations with minor adjustments to the protocol. A specially created bacterial vector into which the desired fragment of the target *LMP1* gene sequence of a given length (799 bp) was cloned was used as a positive control. Deionized water was used as a negative control. The presence of the target PCR product was assessed visually after separation of the amplicons in a 1.5% agarose gel using a 100 bp+ DNA length marker (Qiagen, Germany) (Fig. 2). For subsequent sequencing, the PCR products were purified using the Clean up mini kit (Eurogen, Russia).

LMP1 sequencing

Sanger sequencing of *LMP1* gene samples was performed on an ABI PRISM 3500 instrument (8 capillaries; 50 cm; Applied Biosystems, USA) using a pair of primers (Table 2).

The nucleotide sequences of *LMP1* gene samples translated into amino acid residues were analyzed in

Table 2. Nucleotide sequences of outer (ECO3, 8785) and inner (8702, N2) primers used for nested PCR

Таблица 2. Нуклеотидные последовательности внешних (ECO3, 8785) и внутренних (8702, N2) праймеров, используемые при постановке гнездовой ПЦР

Primer Праймер	Subsequence Последовательность
Eco3	tcc-agg-aga-att-ccc-cat-ctc-gag-agt-g
8785	cga-ttt-taa-tct-gga-tgt-att-acc-atg-g
8702	gct-acc-gat-tct-ggc-cat-gaa-tct-gac
N2	ggc-gga-gtc-tgg-caa-cgc-ccg-ggt-cct-tg

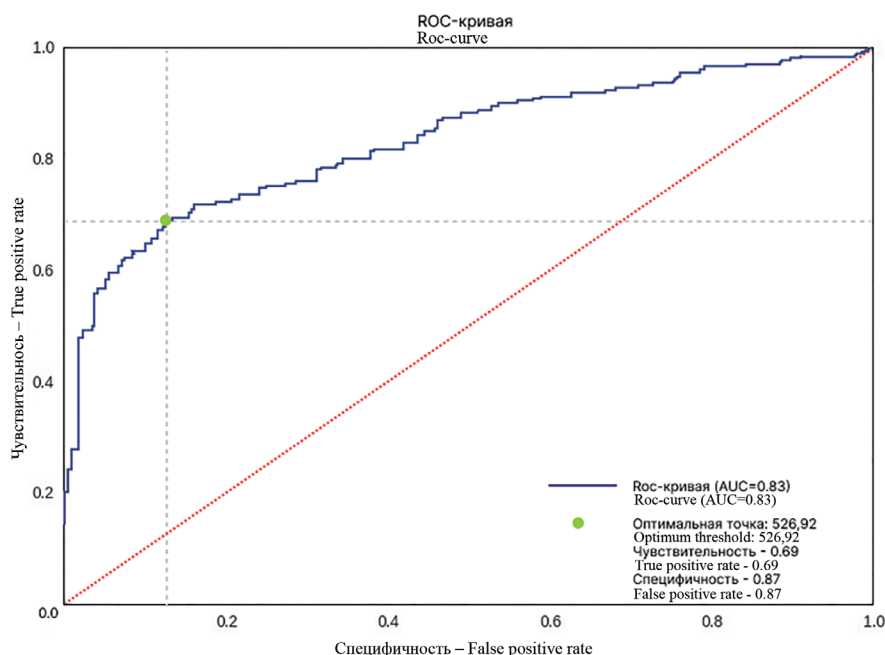


Fig. 3. ROC curve for assessing the prognostic value of Epstein–Barr virus DNA copy number in whole blood for the differential diagnosis of EBV-associated gastric cancer.

AUC = 0.83; optimal threshold: 526.92 copies; sensitivity: 0.69; specificity: 0.87.

Рис. 3. ROC-кривая для оценки прогностической ценности количества копий ДНК вируса Эпштейна–Бarr в цельной крови при дифференциальной диагностике ВЭБ-ассоциированного рака желудка.

AUC = 0,83; оптимальный порог 526,92 копий; чувствительность 0,69; специфичность 0,87.

the SnapGene program using the classification by R.N. Edwards et al. [15].

Statistical analysis

To determine the presence of clinically significant viral load in the blood of patients associated with an increased risk of developing GC, we used a threshold value of DNA copies based on the analysis of the receiver operating characteristic curve (ROC analysis) and the average number of virus DNA copies calculated from all samples studied, taking into account the interquartile range (25th and 75th percentiles).

The χ^2 criterion and Mann–Whitney U criterion were used to assess the statistical significance of differences between groups of samples divided according to the

presence or absence of the desired *LMPI* gene fragment (*LMPI+* and *LMPI-*) in the context of viral load, where the criterion was significant at $p < 0.05$.

Results

Analysis of the optimal threshold value for Epstein–Barr virus copies

The results are presented in the form of ROC analysis conducted on a sample of 227 DNA samples from patients with GC, for whom the viral load was determined by qPCR: AUC (area under the curve) = 0.83; optimal threshold 526.92 copies/reaction; sensitivity 0.69; specificity 0.87 (Fig. 3), as well as descriptive statistics (Table 3), (Fig. 4), including the minimum value of viral

Table 3. Key parameters of viral load distribution across all samples, including minimum and maximum EBV copy numbers, interquartile range, mean, standard deviation, and standard error of the mean, providing a comprehensive description of the sample set

Таблица 3. Ключевые параметры распределения вирусной нагрузки среди всех образцов, включая минимальное и максимальное значения копий ВЭБ, межквартильный размах, среднее, стандартное отклонение и стандартную ошибку среднего, что обеспечивает полное описание выборки

Parameter Параметр	All samples Все образцы
Number of samples Количество образцов	227
Minimum copies of EBV Минимум копий ВЭБ	0
25% Percentile 25% Перцентиль	7.32
Median Медиана	47.5
75% Percentile 75% Перцентиль	172.4
Maximum copies of EBV Максимум копий ВЭБ	27583
Standard value Средняя величина	513.5
Standard deviation Стандартное отклонение	2489
Standard error of the mean Стандартная ошибка среднего	165.2

copies per reaction, median, mean, and interquartile range (IQR). The IQR was $172.4 - 7.32 = 165.08$ copies/reaction.

Determination of the correlation between LMP1 and high viral load of Epstein-Barr virus

Analysis of the relationship between *LMP1* gene detection and viral load in patient blood samples revealed statistical significance using the χ^2 criterion with a significance level of $p = 0.018$ and significant differences according to the Mann–Whitney U test, where $p < 0.0001$ (**Fig. 5**). This result, with a threshold of $p < 0.05$, confirms the existence of a pronounced correlation between the specified parameters.

The selection criterion for analyzing the threshold value of the number of viral DNA copies was based on the average viral load in 227 samples (Table 3) and the optimal threshold of the viral load when constructing the ROC curve (**Fig. 4**). For further molecular analysis, samples with a high viral load exceeding the established threshold of 500 or more EBV copies per reaction ($n = 23$) were selected, which is 10% of the sample and is consistent with the literature data on GC/EBV+ in The Cancer Genome Atlas (The Cancer Genome Atlas, TCGA).

According to our preliminary data, the detection of the *LMP1* gene is associated with a higher probability of high viral load levels in samples (≥ 500 copies of EBV DNA/reaction). According to the results of the study, among 227 blood DNA samples from patients, only in 46 amplification of the *LMP1* gene was successful (*LMP1+*), while in 181 samples *LMP1* gene was not amplified (*LMP1-*). However, only 9 of the 46 DNA samples from *LMP1+* patients had a high viral load of 500 or more EBV copies per reaction (EBV+) (9/46; 19.57%), and among the *LMP1-* samples, only 14 (14/181; 7.72%) were EBV+.

Analysis of mutations in the functional domains of LMP1

Six *LMP1* gene samples that met the established quality criteria from GC patients with high viral load were sequenced using the Sanger method. The nucleotide sequences of these samples were aligned with the reference sequence of the *LMP1* gene of strain B95-8 using SnapGene software, which ensured high-precision identification of nucleotide substitutions. The obtained sequences were translated into amino acids, taking into account the open reading frame, which allowed the predicted structure of the encoded protein to be reconstructed. Particular attention was paid to the detection of amino acid substitutions in functionally significant regions of the protein, in particular in the C-terminal activating domains (CTAR1 and CTAR2). Analysis of nucleotide sequences revealed both synonymous and non-synonymous mutations, including changes that could potentially modulate signal transduction, protein structural stability, or its interaction with cellular adaptors in 4 *LMP1* gene samples (80, 112, 205, 247) out of 6 (**Table 4**).

Table 4 shows that almost half of the mutations (6 out of 13) occur in the C-terminal domain, which may indicate

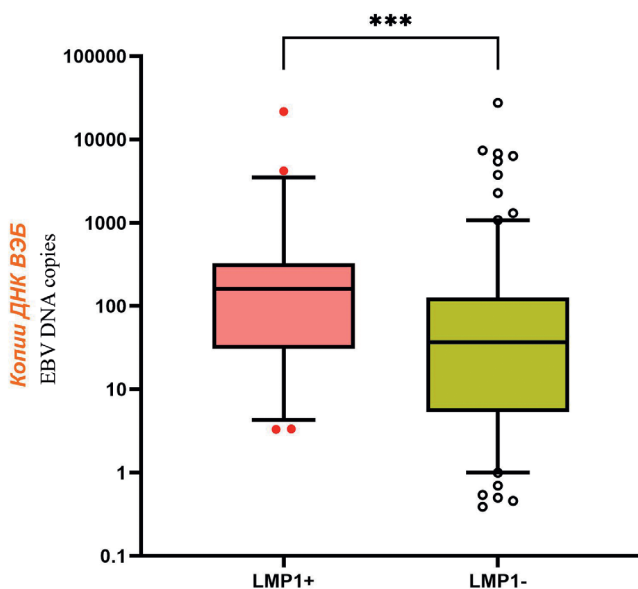


Fig. 4. Distribution of EBV DNA copy numbers across all 227 blood samples from gastric cancer patients, with a minimum value of 0 copies, maximum of 27,583 copies, mean of 513 copies, and median of 47.5 copies.

Рис. 4. Распределение значений копий ДНК вируса среди всех 227 образцов крови больных РЖ, где минимальное значение 0 копий, максимальное – 27 583 копий, средняя величина 513 копий, медиана 47,5 копий.

Table 4. Mutations identified in the nucleotide sequences of the *LMP1* gene in 4 out of 6 analyzed samples, with indication of nucleotide and amino acid changes and their positions in the protein domain structure

Таблица 4. Обнаруженные мутации, выявленные при анализе нуклеотидных последовательностей в 4 из 6 изученных образцов гена *LMP1*, с указанием нуклеотидных и аминокислотных изменений и их положения в доменной структуре белка

Sample number Номер образца	Amino acid position Положение аминокислоты	Nucleotide substitution Замена нуклеотида	Amino acid substitution Замена аминокислоты	Position in the domain Положение в домене
80	284	GAC → GAT	D → D	C-terminal domain С-концевой домен
112	284	GAC → GAT	D → D	C-terminal domain
	211	TCT → TTT	S → F	С-концевой домен STAR1
	375	GAC → AAC	D → N	STAR2
205	287	GAT → ATT	D → I	C-terminal domain
	352	CAT → CAC	H → H	С-концевой домен STAR2
247	215	TCT → TGT	S → C	STAR1
	226, 227	CTG → GTG	L → V	STAR1
	249	CCG → GCG	P → A	STAR1
	259, 270, 297	ACC → AAC	T → N	C-terminal domain С-концевой домен

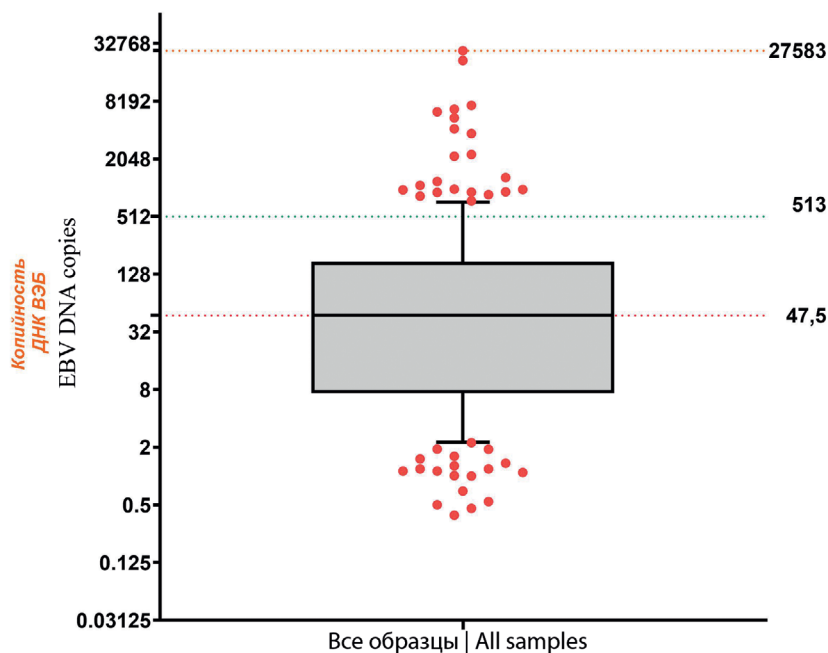


Fig. 5. Statistical significance of differences by the Mann–Whitney U test ($p = 0.0001$), confirming differences in the distribution of quantitative viral load values between *LMP1*-positive (*LMP1*+) and *LMP1*-negative (*LMP1*-) DNA samples from the blood of patients.

Рис. 5. Статистическая достоверность различий по U-критерию Манна–Уитни ($p = 0,0001$), подтверждающая различия в распределении количественных значений вирусной нагрузки между группами *LMP1*-положительных (*LMP1*+) и *LMP1*-отрицательных (*LMP1*-) образцов ДНК крови больных.

its greater susceptibility to mutations in this sample. Most mutations (10 out of 13) are non-synonymous (changing the amino acid), which may affect the structure or function of *LMP1*. Synonymous mutations (3) occur at amino acid positions 284 (2 out of 3) and 352 (1 out of 3).

Discussion

The distribution of the number of EBV copies per reaction in 227 blood DNA samples from patients with GC showed significant variability (Table 3, Fig. 4). The minimum value was 0 copies/reaction, indicating the

absence of detectable EBV copies in some samples, while the maximum reached 27,583 copies/reaction, reflecting rare cases of high viral load. The 25th percentile (Q1) was 7.32 copies/reaction, the median (50th percentile) was 47.5 copies/reaction, and the 75th percentile (Q3) was 172.4 copies/reaction. The interquartile range (IQR = Q3 – Q1) was 165.08 copies/reaction, reflecting the variability of the central 50% of observations and confirming the skewness of the distribution toward lower values. The mean viral load was 513.5 copies/reaction (standard deviation 2489; standard error of the

mean 165.2). The excess of the mean over the median indicates positive asymmetry due to the presence of individual extremely high levels of EBV copy numbers, which is typical for biological data.

ROC analysis was performed for discriminatory assessment of EBV load in the classification of blood samples as EBV-positive and EBV-negative (Fig. 3). The area under the curve (AUC) was 0.83, indicating good diagnostic performance. The optimal threshold for EBV-positive samples, defined as the breakpoint, was 526.92 copies/reaction, with a sensitivity of 0.69 and a specificity of 0.87. This threshold effectively balances false positive and false negative results, prioritizing specificity to minimize unnecessary follow-up testing while capturing a significant proportion of true positive cases.

Based on the integration of descriptive statistics and ROC analysis results, we adopted a viral load threshold of 500 or more copies of EBV/reaction to define EBV-positive samples. This value is close to the optimal threshold obtained by ROC (526.92 copies/reaction) and the sample mean (513.5 copies/reaction), ensuring consistency with the empirical data distribution. It exceeds the upper limit of the IQR (172.4 copies/reaction) by approximately 2.9 times, thereby excluding most samples with low or moderate viral load (75% of the cohort below Q3) and focusing on the segment with a high viral load of more than 513 copies/reaction (Fig. 4), where EBV presumably plays a significant role in the pathogenesis of gastric cancer.

Setting a threshold value of 500 copies/reaction as the criterion for identifying EBV+ blood samples ensures that only viral loads that can be reliably quantified are detected, thereby reducing the likelihood of false-positive results and allowing the detection of clinically significant levels of infection. This methodological approach is fully consistent with established standards in the field of quantitative viral load analysis, where threshold levels are typically determined based on empirical data in order to establish correlations with disease progression or monitor therapeutic interventions in the context of analyzing EBV-associated malignancies.

The results obtained demonstrate a statistically significant association between the detection of the *LMP1* gene and increased EBV load in the blood of patients with GC. Although GC/EBV+ is usually described as type I latency with limited expression of viral genes (EBERs, EBNA1, BART microRNA), the detection of *LMP1* in 19.57% of patients with high viral load in the blood indicates a more active viral profile of the tumor, accompanied by elements of type II latency. These results confirm recent data that GC/EBV+ does not always strictly correspond to the classic type I latency, but rather represents an intermediate state with manifestations of both types of latency, which is important for understanding its pathogenesis [16].

The detection of the *LMP1* gene is associated with a more than twofold increase in the proportion of GC cases with high viral load in the blood compared to *LMP1*-negative samples (19.57% vs. 7.72%), which highlights the potential role of this oncogene not only

as a marker of transformation, but also as an indicator of viral replication activity. The increased viral load in *LMP1*+ patients may reflect either an expanded spectrum of viral gene expression in the tumor or the presence of circulating *LMP1*-expressing cells outside the tumor tissue, for example, in peripheral blood B lymphocytes.

The statistically significant difference found ($p = 0.018$) indicates a correlation between the *LMP1* gene expression and the viral load in blood samples from patients with GC. Thus, the results obtained indicate an association of *LMP1*+ samples with an increased viral load (more than 500 copies per reaction), since 9 out of 46 samples with *LMP1*+ (9/46; 19.57%) were EBV+ (high viral load), while among *LMP1*- (181 samples) only 14 (7.72%) were EBV+. These data suggest that determining the *LMP1* gene sequence in a patient's blood increases the likelihood of a higher viral load in the sample. It should be noted that differences between the *LMP1*+ and *LMP1*- groups, as well as in viral load levels, may be due to other unaccounted factors, such as the state of the patient's immune system, the duration of the disease, or therapeutic intervention.

Sequencing of the *LMP1* gene in blood DNA samples with high viral load in 4 out of 4 cases revealed the presence of key mutations in the C-terminal region, including transactivation domains (Table 4). Sequence analysis revealed both synonymous mutations, which do not lead to changes in the amino acid sequence but are also capable of disrupting protein function, and non-synonymous mutations, which lead to the replacement of one amino acid with another. Synonymous mutations in regulatory regions of the *LMP1* gene disrupt the functional activity of the LMP1 protein by affecting splicing, mRNA stability, or translation rate, which potentially modulates the expression, folding, and immunogenicity of LMP1 in the context of EBV-associated carcinogenesis [17]. In *LMP1* gene samples 80 and 112 (Table 4), such a synonymous mutation (D284D) is located in the intermediate region between the CTAR1 and CTAR2 domains. Although the intermediate position is not part of the classical activation domains, this region mediates LMP1 signals by binding adapter molecules to the activation domains of the C-terminal region, including factors associated with TRAF [18]. The regions between two domains (CTAR1 and CTAR2) have non-synonymous mutations in *LMP1* gene samples 205 and 247: D287I, P249A, T259N, T270N, T297N. Such changes potentially reduce NF- κ B or JNK activation, affect protein stability, its subcellular localization, and signaling activity, especially if the mutations cause conformational rearrangements near the CTAR domains [19].

Mutations in *LMP1* gene samples 112 and 247 (S211F, S215C, L226V, and L227V) are located in the functionally important CTAR1 domain of the LMP1 protein and may lead to impaired interaction with the adapter proteins TRAF1, TRAF2, TRAF3, and TRAF5, which weakens the activation of key signaling pathways—NF- κ B, PI3K/Akt, and MAPK. This reduces the ability of LMP1 to support cell survival, stimulate proliferation, and induce the transformation of fibroblasts and B lymphocytes [20, 21].

The synonymous mutation of the *LMP1* 205 gene (H352H) and the non-synonymous mutation of sample 112 (D375N) are located in the functional domain CTAR2. Mutations in this region lead to impaired interaction with the TRADD and BS69 adapter proteins, as well as weakened recruitment of TRAF2 and TRAF6, which reduces the effectiveness of canonical NF- κ B pathway activation and the JNK signaling cascade [22]. Since these pathways are involved in the induction of inflammatory mediators, regulation of cellular stress, and suppression of apoptosis, their dysfunction may weaken the pro-inflammatory activity of LMP1 and reduce the ability of tumor cells to evade immune control. However, although polymorphisms in CTAR2 functional domain do not affect B-lymphocyte transformation to the same extent as polymorphisms in CTAR1 domain, they contribute to the development of the oncogenic activity of LMP1. At the same time, mutations in these regions of the *LMP1* gene may be associated with reduced tumor aggressiveness and a more favorable prognosis in EBV-associated diseases [20].

Conclusion

The study found a statistically significant correlation between *LMP1* gene sequence amplification and high EBV DNA copy number in the peripheral blood of patients with GC. These results indicate that the presence of this gene is associated with a more active viral profile, which is consistent with current literature data indicating the presence of a dual form of EBV latency in GC.

Sequencing of the *LMP1* gene from blood samples of patients with GC with high EBV DNA concentrations revealed functionally significant changes in the C-terminal region of the protein, including both non-synonymous and synonymous substitutions affecting its regulatory regions. These data indicate that even when the *LMP1* gene is detected, the oncogenic activity of the *LMP1* protein may be altered due to the accumulation of mutations, which may affect the clinical course of the disease.

The results obtained expand our understanding of the heterogeneous molecular nature of EBV+/GC at the level of polymorphism of the key oncogene *LMP1* and emphasize the need for further study of *LMP1* genetic polymorphism and its functional impact on the pathogenesis of EBV-associated gastric tumors.


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Information about the authors:

Alexandra S. Vasilyeva  – Junior Researcher, Laboratory of Biology of Virus-Associated Tumors, Department of Experimental Tumor Biology, Research Institute of Experimental Oncology and Carcinogenesis, N.N. Blokhin National Medical Research Center of Oncology of the Ministry of Health of the Russian Federation, Moscow, Russia; Laboratory of RNA-Containing Viruses I.I. Mechnikov Research Institute of Vaccines and Sera, Moscow, Russia. E-mail: vasilyevaalex23@gmail.com; <https://orcid.org/0009-0004-0249-4574>

Alina A. Margusheva – Postgraduate Student, Department of Antitumor Drug Therapy No. 2, N.N. Blokhin National Medical Research Center of Oncology of the Ministry of Health of the Russian Federation, Moscow, Russia. E-mail: a.margusheva@mail.ru; <https://orcid.org/0000-0002-2397-0304>

Artem D. Molchanov – Junior Researcher, Laboratory of Biology of Virus-Associated Tumors, Department of Experimental Tumor Biology, Research Institute of Experimental Oncology and Carcinogenesis; Postgraduate Student N.N. Blokhin National Medical Research Center of Oncology of the Ministry of Health of the Russian Federation, Moscow, Russia; I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), Moscow, Russia. E-mail: m.artem.aug@gmail.com; <https://orcid.org/0000-0001-5229-2285>

Artem A. Rtishchev – Researcher, Laboratory of RNA-Containing Viruses I.I. Mechnikov Research Institute of Vaccines and Sera, Moscow, Russia. E-mail: rtishchevartyom@gmail.com; <https://orcid.org/0000-0002-4212-5093>

Bogdan S. Cherepovich – Candidate of Medical Sciences, Junior Researcher, Laboratory of RNA-Containing Viruses I.I. Mechnikov Research Institute of Vaccines and Sera, Moscow, Russia. E-mail: bogdancherepovich@mail.ru; <https://orcid.org/0000-0002-5803-6263>

Valeria A. Domanskaya – Research Laboratory Assistant, Laboratory of Biology of Virus-Associated Tumors, Department of Experimental Tumor Biology, Research Institute of Experimental Oncology and Carcinogenesis; Student N.N. Blokhin National Medical Research Center of Oncology of the Ministry of Health of the Russian Federation, Moscow, Russia; I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russian Federation (Sechenov University), Moscow, Russia. E-mail: vadlab@list.ru; <https://orcid.org/0009-0001-4657-382X>

Vladimir E. Gurtsevich – Chief Scientific Consultant, Doctor of Medical Sciences, Professor, Laboratory of Biology of Virus-Associated Tumors, Department of Experimental Tumor Biology, Research Institute of Experimental Oncology and Carcinogenesis N.N. Blokhin National Medical Research Center of Oncology of the Ministry of Health of the Russian Federation, Moscow, Russia. E-mail: gurtsevitch-vlad-88@yandex.ru; <https://orcid.org/0000-0003-1840-4364>

Ksenia V. Smirnova – Candidate of Biological Sciences, Head of the Laboratory of Biology of Virus-Associated Tumors, Department of Experimental Tumor Biology, Research Institute of Experimental Oncology and Carcinogenesis N.N. Blokhin National Medical Research Center of Oncology of the Ministry of Health of the Russian Federation, Moscow, Russia. E-mail: skv.lab@yandex.ru; <https://orcid.org/0000-0001-6209-977X>


Contribution: Vasilyeva A.S. – organization of the study, EBV DNA amplification by qPCR, analysis of the obtained results, manuscript writing; Margusheva A.A. – clinical support of patients and provision of clinical material; Molchanov A.D. – statistical analysis of data; Rtishchev A.A. – performance of genetic engineering work; Cherepovich B.S. – preparation of figures and graphs; Domanskaya V.A. – processing of biological material, LMP1 gene amplification by nested PCR; Gurtsevich V.E. – manuscript editing; Smirnova K.V. – study conception.

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Информация об авторах:

Васильева Александра Сергеевна  – младший научный сотрудник лаборатории биологии вирус-ассоциированной опухоли, отдела экспериментальной биологии опухоли НИИ экспериментальной онкологии и канцерогенеза ФГБУ «НМИЦ онкологии им. Н.Н. Блохина» Минздрава России, Москва, Россия; лаборатории РНК-содержащих вирусов ФГБНУ «НИИ вакцин и сывороток им. И.И. Мечникова», Москва, Россия. E-mail: vasilyevaalex23@gmail.com; <https://orcid.org/0009-0004-0249-4574>

Маргушева Алина Альбертовна – аспирант отделения противоопухолевой лекарственной терапии № 2 ФГБУ «НМИЦ онкологии им. Н.Н. Блохина» Минздрава России, Москва, Россия. E-mail: a.margusheva@mail.ru; <https://orcid.org/0000-0002-2397-0304>

Молчанов Артем Дмитриевич – младший научный сотрудник лаборатории биологии вирус-ассоциированной опухоли, отдела экспериментальной биологии опухоли НИИ экспериментальной онкологии и канцерогенеза; аспирант ФГБУ «НМИЦ онкологии им. Н.Н. Блохина» Минздрава России, Москва, Россия; ФГАОУ ВО Первый МГМУ им. И.М. Сеченова Минздрава России (Сеченовский Университет) Минздрава России, Москва, Россия. E-mail: m.artem.aug@gmail.com; <https://orcid.org/0000-0001-5229-2285>

Ртищев Артем Андреевич – научный сотрудник лаборатории РНК-содержащих вирусов ФГБНУ «НИИ вакцин и сывороток им. И.И. Мечникова», Москва, Россия. E-mail: rtishchevartyom@gmail.com; <https://orcid.org/0000-0002-4212-5093>

Черепович Богдан Сергеевич – канд. мед. наук, младший научный сотрудник лаборатории РНК-содержащих вирусов ФГБНУ «НИИ вакцин и сывороток им. И.И. Мечникова», Москва, Россия. E-mail: bogdancherepovich@mail.ru; <https://orcid.org/0000-0002-5803-6263>

Доманская Валерия Александровна – лаборант-исследователь лаборатории биологии вирус-ассоциированной опухоли, отдела экспериментальной биологии опухоли НИИ экспериментальной онкологии и канцерогенеза; студент ФГБУ «НМИЦ онкологии им. Н.Н. Блохина» Минздрава России, Москва, Россия; ФГАОУ ВО Первый МГМУ им. И.М. Сеченова Минздрава России (Сеченовский Университет) Минздрава России, Москва, Россия. E-mail: vadlab@list.ru; <https://orcid.org/0009-0001-4657-382X>

Гурцевич Владимир Эдуардович – главный научный консультант, д-р мед. наук, профессор лаборатории биологии вирус-ассоциированной опухоли, отдела экспериментальной биологии опухоли НИИ экспериментальной онкологии и канцерогенеза ФГБУ «НМИЦ онкологии им. Н.Н. Блохина» Минздрава России, Москва, Россия. E-mail: gurtsevitch-vlad-88@yandex.ru; <https://orcid.org/0000-0003-1840-4364>

Смирнова Ксения Валерьевна – канд. биол. наук, заведующая лабораторией биологии вирус-ассоциированной опухоли, отдела экспериментальной биологии опухоли НИИ экспериментальной онкологии и канцерогенеза ФГБУ «НМИЦ онкологии им. Н.Н. Блохина» Минздрава России, Москва, Россия. E-mail: skv.lab@yandex.ru; <https://orcid.org/0000-0001-6209-977X>

Участие авторов: Васильева А.С. – организация исследования, амплификация ДНК ВЭБ методом qPCR, анализ полученных результатов, написание рукописи; Маргушева А.А. – клиническое сопровождение больных и обеспечение клиническим материалом; Молчанов А.Д. – статистический анализ данных; Ртищев А.А. – проведение генно-инженерных работ; Черепович Б.С. – оформление рисунков и графиков; Доманская В.А. – обработка биологического материала, амплификация гена *LMP1* методом гнездовой ПЦР; Гурцевич В.Э. – научное редактирование рукописи; Смирнова К.В. – идея исследования.

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