http://dx.doi.org/10.7124/bc.000B2B
UDC 617.7-002.2:575.1

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THE ANALYSIS FOR THE ASSOCIATION OF POLYMORPHIC VARIANTS OF THE VDR GENE (RS2228570) WITH THE RISK OF HERPETIC KERATITIS OCCURRENCE AFTER COVID-19

Aim. *To investigate the association between polymorphic variants of the VDR gene rs2228570 and clinical features of herpetic keratitis in adult patients who have had COVID-19.* ***Methods.*** *Peripheral blood samples from patients (N = 50) with a history of herpetic keratitis that developed after COVID-19 were studied. In comparison with (N = 104) unrelated healthy controls. DNA samples were isolated by lymphocyte lysis with proteinase K followed by the use of DNA purification kit ("MBA LABS"). Analysis of the VDR gene (rs2228570) was performed using fluorescently labeled TaqMan probes manufactured by Thermo Fisher Scientific (USA). Statistical analysis was performed using Fisher's exact test.* ***Results.*** *The results of genotyping followed by comparative statistical analysis revealed significant differences in frequencies of both homozygous genotypes between patients with recurrent HK and controls ($p = 0.01636$). The GG genotype was significantly more common in the recurrent HK group. Importantly, the frequency of A allele carriers (AA+GA) was statistically significantly higher in the control group ($p < 0.05$), OR = 0.3381 with 95% CI (0.1433–0.797).* ***Conclusions.*** *It was shown that the G allele of the FokI VDR gene (rs2228570) polymorphism is associated with recurrent herpetic keratitis in patients from Ukraine, indicating it as a marker of hereditary predisposition to the development of recurrent herpetic keratitis after COVID-19.*

Keywords: *herpetic keratitis, COVID-19, genetic marker, VDR gene.*

Citation: Mohylevets A.O., Sereda E.V., Drozhzhyna G.I., Livshyts G.B., Gorodna O.V., Livshits L.A. (2025) The analysis for the association of polymorphic variants of the VDR gene (rs2228570) with the risk of herpetic keratitis occurrence after COVID-19. *Biopolymers & Cell*, 4(41), 283—291. http://dx.doi.org/10.7124/bc.000B2B

Introduction

Herpetic keratitis (HK) is one of the most common infectious diseases of the cornea, which can lead to the vision impairment or complete loss of vision [1]. The disease is caused by the herpes simplex virus (HSV), which infects the cornea, causing primary or subclinical infection that may transition into a latent stage in sensory ganglia, primarily the trigeminal ganglion, making the host a lifelong carrier [2]. Reactivation of the virus from latency triggers recurrent episodes of keratitis, accompanied by pronounced inflammatory response, corneal tissue damage, scar formation, and risk of blindness. Liesegang *et al.* [3] demonstrated that the recurrence rate of ocular infection caused by herpes simplex virus is 9.6% within the first year after the initial episode and increases to 63.2% over 20 years. Currently, herpetic keratitis has gained relevance in the context of the COVID-19 pandemic, as the disease caused by the SARS-CoV-2 virus is characterized by a systemic inflammatory syndrome ("cytokine storm" with excess IL-6, IL-1β, TNF-α), lymphopenia (reduction in CD4+ and CD8+ T-lymphocytes, natural killers), and immunosuppression. These factors create conditions for the reactivation of latent herpesviruses, including HSV-1, which is supported by clinical observations: cases of herpetic keratitis, particularly stromal, have been recorded in patients with COVID-19 both during and after the infection [4, 5]. One of the key factors influencing immune regulation is the active form of vitamin D (1,25-dihydroxyvitamin D3, or calcitriol), which binds to the vitamin D receptor (VDR), providing an immunomodulatory effect, including inhibition of pro-inflammatory cytokine production (IL-2, IFN-γ), stimulation of anti-inflammatory cytokine secretion (IL-10), as well as regulation of angiogenesis and healing of corneal damage [6]. The VDR gene (Vitamin D Receptor) is located on chromosome 12q13.11 and consists of 14 exons [7, 8]. It encodes a nuclear receptor for vitamin D, which is expressed in epithelial cells and stromal keratocytes of the cornea, indicating its involvement in local tissue protection mechanisms. The VDR expression has been detected in various immune cells, including peripheral blood mononuclear cells enriched with monocytes, as well as macrophages, dendritic cells, natural killer cells (NK), and invariant natural killer T cells (iNKT) [9—14]. Due to these properties, vitamin D and its receptor play a crucial role in maintaining the balance between effective antiviral defense and prevention of severe forms of HK. In the first exon of the VDR gene, there is a single nucleotide variant rs2228570 (also known as FokI). This variant is located in the start codon and causes a shift in the translation initiation site. It has been established that FokI is the only VDR polymorphism that alters the protein length and leads to functional consequences, such as vitamin D deficiency or excessive formation and/or denaturation of the active form of vitamin D [15]. As a result of substituting the start triplet ATG with ACG, the translation initiation site shifts one triplet downstream. Consequently, the protein product of the VDR gene is shortened by three amino acid residues. Thus, two protein forms exist: the long form (produced from the f/AA allele) and the short form (produced from the F/AG or GG allele). The longer variant contains 427 amino acids and is designated as the M1 form, as translation starts from the first methionine. The shorter variant contains 424 amino acids and is designated as the M4 form, where translation begins from the fourth methionine [16]. This genetic variation is associated with changes in the transcriptional activity of the receptor protein, which may influence susceptibility to viral infections, such as herpes simplex keratitis, especially under immunosuppression caused by COVID-19.With the meta-analysis, Laplana *et al.* (2018) established that the FokI rs2228570 polymorphism is associated with susceptibility to infectious diseases, particularly carriers of the A-allele have an increased risk of severe infection caused by respiratory syncytial virus (RSV) [17]. He *et al.* [18] found that this polymorphism was also a potential risk factor for hepatitis B virus (HBV) infection, affecting disease progression.

In the context of chronic hepatitis C virus (HCV) infection, Thanapirom *et al.* [19] showed that FokI rs2228570 AA/GA genotypes were independent predictors of advanced liver fibrosis in Thai patients, indicating their impact on the severity of liver pathology through reduced VDR transcriptional activity. Regarding herpetic keratitis (HK), the influence of the rs2228570 polymorphism may theoretically also be significant, as VDR plays a key role in the regulation of immune response, which is critical for controlling herpes simplex virus (HSV-1). Extensive study of the relationship between the FokI rs2228570 polymorphism, clinical manifestations of herpes simplex keratitis, and immunosuppression caused by prior COVID-19 may contribute to the development of personalized approaches to diagnosis, treatment, and prevention of this disease.

Aim. To investigate the association between polymorphic variants of the VDR gene rs2228570 and clinical features of primary and recurrent herpetic keratitis in adult patients who have had COVID-19.

Materials and Methods

Peripheral blood samples from the patients (N = 50), with a mean age of 55 years, who had a history of herpetic keratitis with various courses that developed after laboratory-confirmed COVID-19 of varying severity (mild, moderate-severe) were used for the study. The laboratory data and detailed clinical characteristics of the patients included in this study, described earlier, suggested reactivation of latent herpes infection in the patients who had COVID-19. Since the IgG levels in the venous blood to HSV1-2 viruses were significantly increased compared to the reference values [20]. It is also important to note that the serum vitamin D amount in blood of the majority of patients was below normal and only in 12.5% of patients had normal level [20]. As a control, the genotyping data from a population group (N = 104) of healthy unrelated individuals from various regions of Ukraine, obtained from the Human Genomics Laboratory database of the Institute of Molecular Biology and Genetics of the National Academy of Sciences of Ukraine under project № 0123U102780, were used. The patients with HK were divided into two groups: the first group with primary HK (N = 16) and the second group with recurrent HK (N = 34). The clinical and anamnestic data of patients (severity of COVID-19, form of herpetic lesion) were obtained during outpatient and inpatient examinations and confirmed by PCR testing results. Blood samples from patients were provided by the State Institution "Institute of Eye Diseases and Tissue Therapy named after V.P. Filatov of the National Academy of Medical Sciences of Ukraine" (Odesa). The whole blood collection with ethylenediaminetetraacetic acid (EDTA) (2 ml) was performed in accordance with basic bioethical rules, after obtaining informed consent for the study from all participants. The study plan was approved by the Bioethics Committee of the State Institution "Institute of Eye Diseases and Tissue Therapy named after V.P. Filatov of the National Academy of Medical Sciences of Ukraine" (09.07.2024/№ 5). Analysis of the FokI single nucleotide polymorphism (rs2228570 A>G) of the VDR gene was performed using real-time polymerase chain reaction (PCR) with fluorescently labeled TaqMan probes on the iQ5TM Multicolor Real-Time PCR Detection System (BIO-RAD, USA) [21, 22]. A reagent kit for genotyping FokI (rs2228570) of the VDR gene, manufactured by Thermo Fisher Scientific (USA), was used. Genotyping was performed by registering fluorescence signals in real time using Bio-Rad iQ5 Optical System Software, which allowed plotting the dependence of fluorescence intensity in the sample on the number of DNA amplification cycles. As a result of the analysis of real-time amplification curves, all polymorphic variants for the FokI rs2228570 (A>G) single nucleotide variant of the VDR gene were identified.

Statistical processing of results

Comparison of the distribution of genotypes and allelic variants between groups of patients with HK

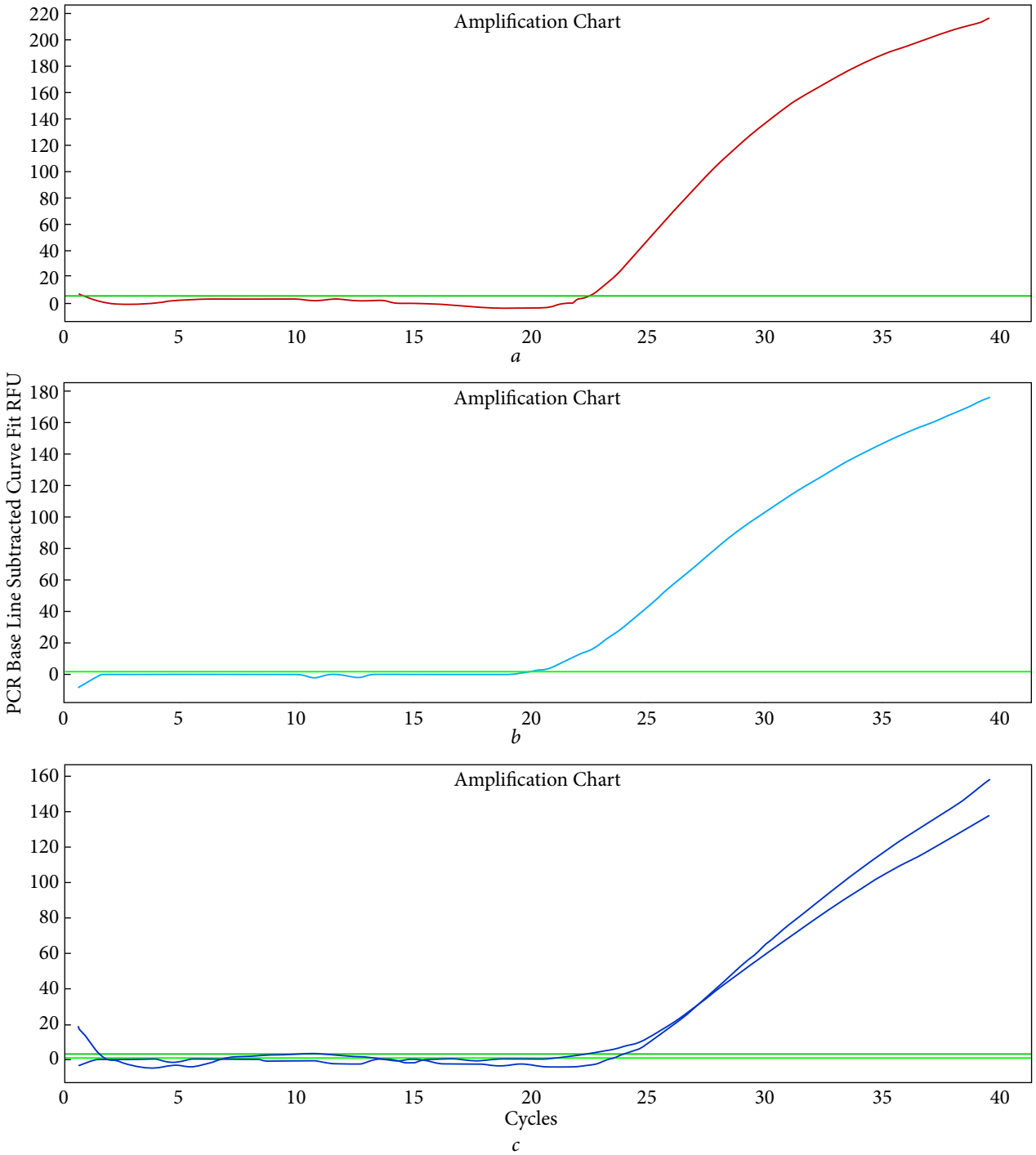

Fig. 1. Fluorescence amplification curves for the VDR gene genotyping (rs2228570). Genotypes identified in the patients with herpetic keratitis and control group. *a* — Homozygote AA: Dependence of fluorescence intensity in the sample on the number of DNA amplification cycles. *b* — Homozygote GG: Dependence of fluorescence intensity in the sample on the number of DNA amplification cycles. *c* — Heterozygote GA: Dependence of fluorescence intensity in the sample on the number of DNA amplification cycles

and the population control was performed using Fisher's exact test with the online resource OpenEpi. Odds ratios (OR) with 95% confidence intervals (CI) were calculated using the same resource. Statistical significance was considered at $p < 0.05$.

Results

The analysis of genotypes and allelic frequencies of the VDR gene (rs2228570) was conducted in a group of patients with herpetic keratitis (HK) and in a control group of healthy individuals from various regions of Ukraine ("control"). In both the group of patients with keratitis and the control group, all variants of the VDR gene (rs2228570) genotypes were detected. In our study, FAM dye, specific for the G allele, and HEX for the A allele were used as reporters. Thus, detection of fluorescence intensity from one fluorophore indicates homozygosity, while detection of both fluorophores interprets the genotype as heterozygous (Fig. 1).

Comparison of genotype and allele frequencies of the rs2228570 polymorphism of the VDR gene was performed between the group of patients with herpetic keratitis and the population control group (N = 104). For further analysis, patients with herpetic keratitis (HK) were divided by clinical subtypes of disease course into two groups: primary HK (N = 16) and recurrent HK (N = 34). The results of the distribution of genotypes and alleles of the VDR gene in groups with different forms of HK and the control group are presented in Table 1.

In the primary HK group, genotype frequencies were distributed as follows: homozygotes GG and heterozygotes GA 37.5% each, genotype AA — 25%. In patients with recurrent HK, the heterozygous genotype AG predominated (50%), followed by GG (38%), and the lowest frequency was observed for AA (12%). In the control group, the most common was the heterozygous genotype AG (55%), followed by AA (28%) and GG (17%). In allelic analysis, it was found that the G allele was more frequent in the recurrent HK group (63.2%) and primary HK (56.3%), while in the control group, the A allele predominated (55.3%). The frequency of the G allele in the control sample was the lowest (44.7%). When conducting statistical analysis using Fisher's exact test, a statistically significant difference was found in the distribution of homozygous genotypes GG and AA between the patients with recurrent HK and the population control ($p = 0.01636$), with the GG genotype significantly more common in the recurrent HK group. When examining odds ratios, the following values were obtained: OR = 2.958 with 95% CI (1.254—6.977).

Comparative analysis was performed for the G allele carriers (GG+GA) and the A allele carriers (AA+GA) in the patients with recurrent HK and the individuals of control group. The results of the distribution of the proportion of A and G allele carriers of the VDR gene are presented in Tables 2 and 3, respectively.

The frequency of A allele carriers (AA+GA) was statistically significantly higher in the control

Table 1. **Distribution of frequencies of genotypes and alleles of the FokI rs2228570 (A>G) polymorphism of the VDR gene in patients with primary and recurrent HK and the control population group**

Locus VDR, A/G	Overall group with HK, n = 50	Primary, n = 16	Recurrent, n = 34	Population control, n = 104
Genotypes, n (%)				
AA	8 (0.16)	4 (0.25)	4 (0.12)	29 (0.28)
AG	23 (0.46)	6 (0.375)	17 (0.5)	57 (0.55)
GG	19 (0.38)	6 (0.375)	13 (0.38)	18 (0.17)
Alleles				
A	0.39	0.437	0.368	0.553
G	0.61	0.563	0.632	0.447

group ($p < 0.05$). Odds ratio OR = 0.3381 with CI (0.1433—0.797), 95%. One the other hand, comparative analysis for G-allele carriers (GG+GA), revealed the trend toward an association between of G-allele with the recurrent form of HK ($p = 0.0535$). The results obtained in our study demonstrate a statistically significant increase in the frequency of the G allele in patients with recurrent HK compared to individuals in the control group. Thus, carriage of the G allele may be considered as a factor of hereditary predisposition to the development of recurrent herpetic keratitis.

Discussion

During the study, the association was established between the FokI polymorphism of the vitamin D receptor gene and the course of HK in adult patients who had COVID-19 of varying severity. The results indicate that carriage of the shorter isoform of the G allele of the VDR gene is 2.2 times more likely in the recurrent HK group than in the control (38% vs. 17%). Several functional studies have shown that the shorter 424-aa isoform corresponding to the G (or F) allele exhibits increased transactivation activity, which can be explained by more efficient interaction with transcription factors (such as TFIIB), the formation of an active VDR-RXR heterodimer — the main complex that binds to vitamin D response elements (VDRE) and regulates the transcription of target genes — as well as greater isoform stability compared to the longer form associated with the A (or f) allele [23, 24]. The immune response in herpetic corneal damage is dual: on one hand, effective antiviral activity is needed; on the other, control over inflammation to avoid autoimmune or excessive tissue damage. Vitamin D, through binding to VDR, regulates the expression of antimicrobial peptides (including cathelicidins), interleukins (IL-10, IL-6), and other cytokines involved in modulating innate and adaptive immunity [9, 11, 14]. The short variant of VDR, encoded by the G allele, may promote increased production of pro-inflammatory cytokines (e.g., IL-6, TNF-α), which are key mediators of the cytokine storm characteristic of severe COVID-19. In corneal tissue cells, such immune hyperreactivity may lead to chronic inflammation, epithelial destruction, and recurrences of herpetic keratitis, even with minimal viral load. Additionally, the response of Th17 cells, a subpopulation of $CD4^+$ T-lymphocytes enhanced by IL-6 and TGF-β, may be excessively activated, which is also characteristic of autoimmune-like corneal damage [25]. The FokI polymorphism of the VDR gene (G/A allele, rs2228570) has been extensively studied in the context of various infectious and autoimmune diseases. On the one hand, there are studies supporting the association of the "unfavorable" allele (corresponding to the G allele in our work) with increased risk or more severe course of immune-mediated diseases. For rheumatoid arthritis (RA), most studies (including several meta-analyses) have shown that carriers of the G variant of the FokI polymorphism have a higher predisposition to developing RA [26]. Specifically, the F allele (corresponding to the G allele — short active receptor isoform) and FF/Ff

Table 2. **Distribution of the proportion of G allele carriers of the VDR gene in the recurrent group and the population control**

Locus VDR, A/G	Recurrent, n = 34	Population Control, n = 104
	Genotypes, n (%)	
GG+GA	30 (0.88)	75 (0.73)
AA	4 (0.12)	29 (0.27)

Table 3. **Distribution of the proportion of A allele carriers of the VDR gene in the recurrent group and the population control**

LocusVDR, A/G	Recurrent, n = 34	Population Control, n = 104
	Genotypes, n (%)	
AA+GA	21 (0.62)	86 (0.83)
GG	13 (0.38)	18 (0.17)

genotypes were associated with increased genetic risk of RA in at least five independent samples [27—31]. At the same time, the opposite homozygous genotype (ff, corresponding to the A allele) was linked to more severe course and disease activity. An additional factor that could have influenced the results is the vitamin D level in the studied individuals. The FokI polymorphism alters receptor activity, but its effect may significantly depend on the body's supply of the ligand — namely, vitamin D. If most participants had similar vitamin D status (e.g., general deficiency or normal level), differences in receptor function might not play a role. It is known that severe deficiency of 25(OH)D3 is associated with worse outcomes of COVID-19, while sufficient levels-with better prognosis, regardless of VDR genotype. Therefore, the genetic effect of FokI may manifest only under certain conditions — for example, at critically low vitamin D levels, when reduced receptor activity further limits the immune response. Importantly, that the levels of vitamin D in the serum of the majority of patients in this study were below normal [20]. Analyzing the role of the G allele (FokI polymorphism) in various studies, it should be emphasized that its influence largely depends on the genetic-demographic context: genetic heterogeneity of populations [32]. The VDR allele frequencies can differ substantially between ethnic groups and may exist in different combinations with other genes that modulate immunity [26]. It has been proven that the distribution of VDR-FokI genotypes varies markedly depending on ethnic origin [32]. So studies conducted in individual countries or groups are not always generalizable to others [32]. Despite the new data obtained, our understanding of the role of VDR polymorphism in antiviral immunity remains far from comprehensive. To increase statistical power, more patients from different regions should be involved. This will allow verification of the reproducibility of the G allele association with herpetic keratitis recurrences. Multicenter studies on different populations will help eliminate ethnic and geographic biases and provide more universal conclusions. Functional tests, such as measuring levels of key cytokines (IL-17, IFN-γ, IL-10, *etc.*) and T-lymphocyte activation markers depending on genotype, will help better define the functional difference between alleles. The studies on corneal cells are also relevant: for example, determining whether the expression of antiviral peptides (cathelicidin LL-37, β-defensins) differs in corneal epithelial cells with different VDR variants upon stimulation with 1,25(OH)2D3. Such studies will confirm or refute the hypothesis that the G allele modulates an aggressive immune response leading to recurrence.

Conclusions

The G allele of FokI polymorphism in the VDR gene was shown to be associated with recurrent herpetic keratitis in the patients from Ukraine, indicating its potential involvement as a factor of hereditary predisposition to the development of recurrent herpetic keratitis after COVID-19.

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Received 14.10.2025

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АНАЛІЗ АСОЦІАЦІЇ ПОЛІМОРФНИХ ВАРІАНТІВ ГЕНА VDR (RS2228570) З РИЗИКОМ ВИНИКНЕННЯ ГЕРПЕТИЧНОГО КЕРАТИТУ ПІСЛЯ COVID-19

Мета. Дослідити зв'язок між поліморфними варіантами гена VDR (rs2228570) та клінічними особливостями герпетичного кератиту у дорослих пацієнтів, які перенесли COVID-19. ***Методи.*** Були досліджені зразки периферичної крові пацієнтів (N = 50) з герпетичним кератитом в анамнезі, що розвинувся після COVID-19. У порівнянні з (N = 104) неспорідненими здоровими контрольними індивідами. Зразки ДНК були виділені шляхом гідролізу лімфоцитарних лізатів протеїназою К з подальшим використанням набору для очищення ДНК «MBA LABS». Аналіз гена VDR (rs2228570) проводили з використанням флуоресцентно мічених зондів TaqMan виробництва Thermo Fisher Scientific (США). Статистичний аналіз проводили за допомогою точного тесту Фішера. ***Результати.*** Результати генотипування з подальшим порівняльним статистичним аналізом виявили значну різницю в частоті обох гомозиготних генотипів між пацієнтами з рецидивуючим герпетичним кератитом та контрольною групою (p = 0,01636). Генотип GG значно частіше зустрічався в групі рецидивуючого герпетичного кератиту. Важливо, що частота носіїв алеля A (AA+GA) була статистично значущо вищою в контрольній групі (p < 0,05), OR = 0,3381 з 95% ДІ (0,1433—0,797). ***Висновки.*** Було показано, що алель G поліморфізму FokI гена VDR (rs2228570) асоційований з рецидивуючим герпетичним кератитом у пацієнтів з України, що визначає його як потенційного маркера спадкової схильності до розвитку рецидивуючого герпетичного кератиту після коронавірусної хвороби.

***Ключові слова*:** герпетичний кератит, COVID-19, генетичний маркер, ген *VDR*.