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IFNL4 rs12979860 polymorphism in patients with herpetic keratitis and a history of COVID-19

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Поліморфізм нуклеотидної послідовності гена IFNL4 (rs12979860) у пацієнтів з герпетичним кератитом після перенесеного COVID-19

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Abstract

Purpose: *To investigate a possible association between IFNL4 rs12979860 variants and susceptibility to herpetic keratitis (HK) in individuals with a history of COVID-19.*

Material and Methods: *The study group included 50 eyes in 50 patients with HK and a history of COVID-19 (16 patients with primary HK and 34 patients with recurrent HK). Patients were genotyped for IFNL4 rs12979860 using Taqman probe real-time polymerase chain reaction. Analysis of amplification curves was performed to obtain all polymorphic variants of IFNL4 SNP rs12979860. Genotyping data of the comparison group (n = 73; women with a history of COVID-19 of various severity but without manifestations of eye disease during hospitalization for COVID-19) were available from project N 0120U104508 and were used for analysis in this study. Genotyping data of the population control group (n = 100) were available from the database of the Human Genomics Laboratory, Institute of Molecular Biology and Genetics, National Academy of Sciences of Ukraine and were used as controls. These groups included healthy individuals from various Ukrainian regions who were not related to each other.*

Results: *Fisher exact test showed a significant difference ($p < 0.05$) in the distribution of genotypes and polymorphic variants (alleles) between the study group and the comparison group and between the study group and the control group. We compared the distribution of genotype and alleles for rs12979860 between patients with recurrent HK and the control group. The homozygous (CC) genotype of rs12979860 was significantly more common in patients with HK.*

Conclusion: *We found an association between the homozygous CC genotype of IFNL4 (SNP rs12979860) with recurrent HK. The C allele could be viewed as a genetic marker of inherited predisposition to HK in individuals with a history of COVID-19.*

Keywords: *herpetic keratitis, COVID-19, gene polymorphism, IFNL4, cornea.*

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Резюме

Мета. *Вивчити можливий зв'язок поліморфізмів C/T rs12979860 гена IFNL4 зі схильністю до розвитку герпетичного кератиту (ГК) у осіб після перенесеного COVID-19.*

Матеріал та методи. *Всього проаналізовано 50 очей у 50 хворих у загальній групі пацієнтів із ГК (n=50), що розвинувся після перенесеної COVID-19 інфекції. Група обстеження включала: а) хворі з первинним ГК після перенесеного COVID-19 (n=16) та б) хворі з рецидивом ГК після перенесеного COVID-19 (n=34). Генотип пацієнта за поліморфізмом гена IFNL4 (rs12979860), визначався методом полімеразної ланцюгової реакції (ПЛР) у реальному часі з використанням флуоресцентно мічених зондів TaqMan. За допомогою аналізу кривих ампліфікації було отримано всі поліморфні варіанти за однонуклеотидним варіантом C/T rs12979860 гена гена IFNL4 (CC, CT, TT). Для аналізу було використано дані генотипування групи порівняння (n=73), що включала жінок, які перенесли COVID-19 різного ступеня тяжкості та не мали проявів очних хвороб, взяті з проекту N 0120U104508. В якості контролю було використано дані генотипування осіб популяційної контрольної групи (n=100), які були отримані з бази даних лабораторії геноміки людини Інституту молекулярної біології та генетики НАН України. Ці групи включали здорових неспоріднених індивідів з різних регіонів України.*

Результати. *В результаті порівняльного аналізу розподілу генотипів та поліморфних варіантів між індивідами з групи обстеження: 1) групою порівняння; 2) контрольною групи за критерієм Фішера – було отримано статистично значущу відмінність (p<0,05). Подібний порівняльний аналіз проводили між індивідами з групи з рецидивуючим ГК та контрольною групою. Частота гомозиготного генотипу CC була вірогідно вищою у групі пацієнтів з ГК.*

Висновки. *Встановлено асоціацію гомозиготних генотипів CC (rs12979860) гена IFNL4 з розвитком рецидивуючого герпетичного кератиту. Алель C можна розглядати в якості генетичного маркера спадкової схильності щодо ризику розвитку герпетичного кератиту у осіб, що перенесли COVID-19.*

Ключові слова: *герпетичний кератит, COVID-19, поліморфізм гена, IFNL4, рогівка*

Introduction

Herpetic keratitis (HK) remains a major cause of vision loss and is a challenge to the ophthalmological community, especially in the context of the COVID-19 pandemic. Immune dysregulation caused by the SARS-CoV-2 virus may trigger the reactivation of latent viral infections, particularly herpetic infections [1, 2].

Herpes simplex virus type 1 (HSV1) keratitis is a leading cause of infectious blindness in developed countries [3-6]. Superficial keratitis lesions are most common corneal lesions in patients with primary HSV-1 keratitis, while herpes stromal keratitis accounts for 20-48% of recurrent cases of ocular HSV infection [7] and is the form of HSV keratitis that is associated with long-term vision loss due to corneal scarring and neovascularization [8].

Ocular manifestations reported in COVID-19 patients include conjunctivitis, anterior uveitis, sclerouveitis, reactivation of inactive anterior uveitis, vitritis, panuveitis, retinal hemorrhage, retinal artery or vein occlusion, multifocal chorioretinitis, and central serous chorioretinopathy [9-13]. In a study by Wu and colleagues [14], a total of 12 of 38 COVID-19 patients (31.6%) had ocular manifestations. COVID-19 is known to be able to contribute to exacerbation of chronic infections particularly herpetic infections. Cases of HK in patients with active COVID-19 infection (possibly due to reactivation of HSV-1 keratitis) have been reported [15].

The immune system of patients with severe COVID-19 exhibits immunosuppression and is characterized by cytokine storm syndrome and low levels of T and natural killer (NK) cells, creating an environment favorable for HSV-1 reactivation. Majtanova et al [3] reported five cases of HSV-1 keratitis in patients who had laboratory-confirmed COVID-19. SARS-CoV-2 infection may be a risk factor for developing HSV-1 keratitis, or it may act as a potential activator of this ocular disease [3]. Aside from environmental factors, patient's genetic features play an important role in the variability of the clinical course of infection. Comprehensive research on the relationship between the clinical manifestations of HK, history of COVID-19 infection, and genetic features is important in the personalized approach to the diagnosis, treatment and prevention of the disease.

Interferons (IFNs) are the first line of defense against pathogens e.g. respiratory viruses. They are key components of the innate immune system and, during the initiation of antiviral immune response, they play an important role in the inhibition of viral replication and are involved in the formation of adaptive immunity [16, 17]. Two types of IFN (type I [IFN-I] and type III [IFN-III or IFN-λ or IFNL) are involved in this process [18].

Studies on the interferon lambda (IFNL) gene polymorphisms demonstrated that polymorphisms in IFNL4, including rs12979860 and rs368234815, were significantly associated with reduced clearance of hepatitis C virus (HCV) and other RNA viruses [19]. Our and others previous studies have shown that this single nucleotide polymorphism (SNP) was associated with sustained virological response in patients with chronic hepatitis C treated with pegylated IFN [20]. Griffiths et al [21] demonstrated that the expression of the IFNL4 gene and the SNP rs12979860 variants were associated with the recurrence and severity of recurrent herpes simplex virus type 1 (HSV-1) disease. The data available provide evidence that rs12979860 does not determine the susceptibility to infection, but primarily

is associated with clearance of the virus and severity of infection.

With this in view, we suppose that single nucleotide polymorphism (SNP) rs12979860 may be considered as a promising genetic marker of susceptibility to viral infection of various severity, particularly, the clinical phenotype in patients with HK and a history of COVID-19. Given the data available today, we focused our study on investigating the association between functionally significant genetic variants of IFNL4 and an increased susceptibility to HK in individuals with a history of COVID-19.

The purpose of the study was to investigate a possible association between IFNL4 rs12979860 variants and susceptibility to HK in individuals with a history of COVID-19.

Material and Methods

Totally, we analyzed 50 eyes in the examination group of patients with HK and a history of COVID-19 infection (n=50), including patients with primary HK (n=16) and those with recurrent HK (n=34). The mean age in both groups was 55 years (SD 14.8). To perform this study, blood samples were obtained from the fifty inpatients treated at the Corneal Pathology Department, SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine".

Inclusion criteria were patients with both HK and a history of COVID-19 infection. Exclusion criteria were patients with diabetes mellitus, autoimmune diseases or immunosuppressive conditions.

The levels of immunoglobulin G (IgG) antibodies against the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) spike receptor-binding domain (S-RBD) in venous blood were measured to confirm a history of COVID-19 infection. Sample values of 40-50 AU/ml were classified as borderline, and values of > 50AU/ml, positive for anti-SARS-CoV-2 IgG antibodies.

Patients were divided into those with a history of mild COVID-19 infection (without evidence of viral pneumonia) and those with a history of moderate-to-severe COVID-19 infection (with pneumonia not treated at the intensive care unit) [22].

Additionally, they were divided into those with dendritic HK, those with non-necrotizing stromal HK and those with ulcerative necrotizing HK according to Liesegang's classification [23].

Genotyping data of the comparison group (n = 73; women with a history of COVID-19 of various severity but without manifestations of eye disease during hospitalization for COVID-19) were available from project N 0120U104508 and were used for analysis in this study. Genotyping data of the population control group (n = 100) were available from the database of the Human Genomics Laboratory, Institute of Molecular Biology and Genetics, National Academy of Sciences of Ukraine and were used as controls. These groups included healthy individuals from various Ukrainian regions who were not related to each other.

Therefore, the study involved three groups, namely (i) the study group of patients with both HK and a history of COVID-19, (ii) the comparison group and (iii) the population control group.

Whole peripheral blood samples were collected in tubes containing ethylenediaminetetraacetic acid (EDTA) to extract DNA from leucocytes while complying with bioethical standards.

DNA samples were number coded to provide for easy identification and to create and preserve anonymity. This study was approved by the Ethics committee of SI "The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine" (committee meeting minutes of September 8, 2025) and written informed consent was obtained from all study subjects.

Patients were genotyped for IFNL4 rs12979860 using Taqman probe real-time polymerase chain reaction (PCR) [24] (TaqMan SNP Genotyping Assay, Thermo Fisher Scientific, Waltham, MA). During PCR amplification, Taq DNA polymerase with 3-5 exonuclease activity degrades probes attached to amplified templates, separating the reporter fluorochrome (e.g., fluorescein amidite [FAM] or VIC) and quencher (tetramethylrhodamine [TAMRA]). As a result, fluorescence intensity rises proportionally to the number of amplified DNA copies and is recorded in real time. In order to perform the genotyping of the samples, two dyes were used, VIC and FAM. One is specific for the C allele (VIC), while the other is specific for the T allele (FAM).

Statistics. The study group and control groups were compared for distribution of genotypes and polymorphic variants (alleles) using Fisher exact test and OpenEpi (openepi.com). Odds ratios (OR) and 95% confidence intervals (CI) were calculated using OpenEpi.

Results

Host SNP genotyping at rs12979860 C/T was performed in patients with primary or recurrent HK (n = 50) that had a history of COVID-19 of various severity. Analysis of amplification curves was performed to obtain all variants of IFNL4 rs12979860.

The reaction mix contained primers and two fluorescence labeled TaqMan probes; one probe was used for each allele. The cycle number during the PCR run is depicted on the X axis; fluorescence intensity on the Y axis directly reflects the accumulation of amplified DNA. Following PCR, an increase in the level of an FAM fluorescent signal without a rise in the VIC specific signal indicates that only the FAM specific sequence (allele) was present and that the sample is homozygous (Fig. 1 (homozygous TT genotype)). An increase in the level of an FAM fluorescent signal with a rise in the VIC specific signal indicates that both the T and C alleles were present and that the sample is heterozygous (Fig. 2 (heterozygous TC genotype)). An

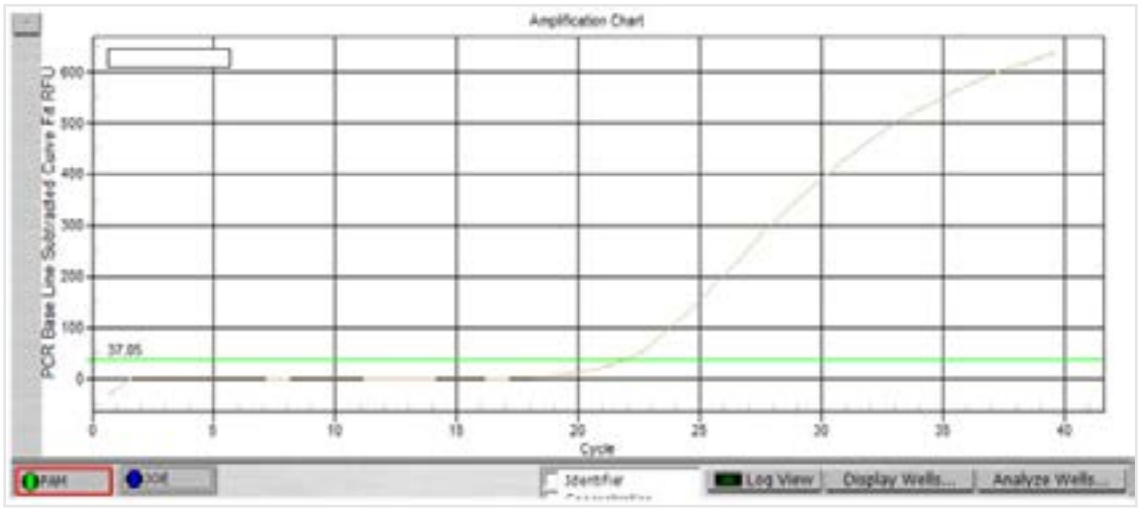

Fig. 1. Homozygous TT genotype. Fluorescence intensity against the number of DNA amplification cycles.

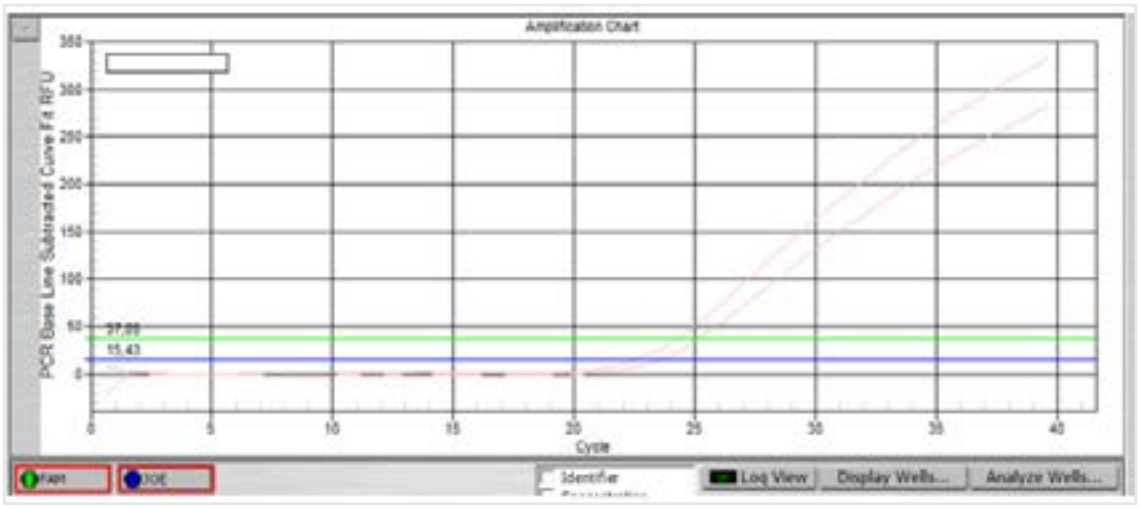

Fig. 2. Heterozygous TC genotype. Fluorescence intensity against the number of DNA amplification cycles.

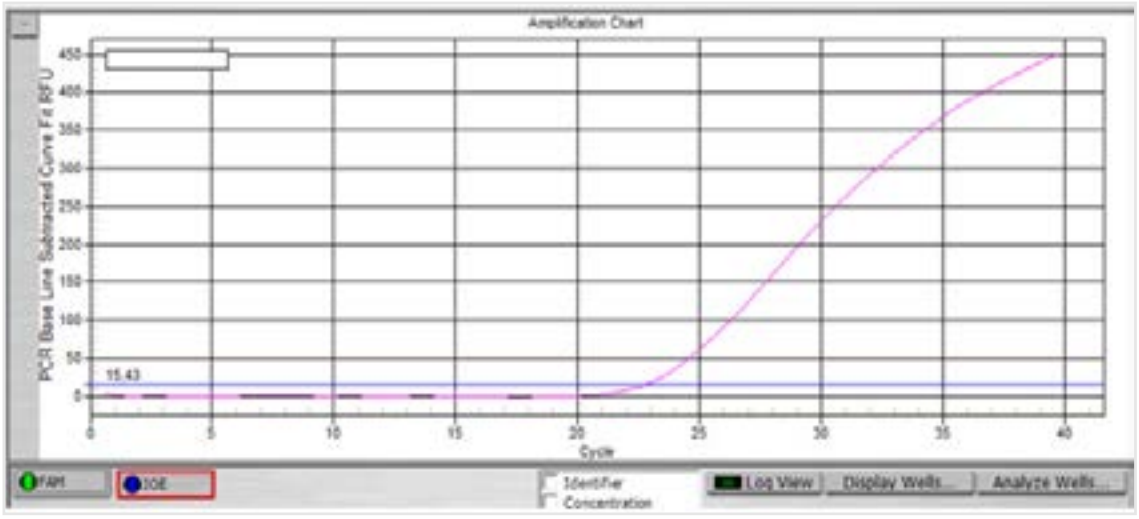

Fig. 3. Homozygous CC genotype. Fluorescence intensity against the number of DNA amplification cycles.

increase in the level of a VIC-specific fluorescent signal without a rise in the FAM specific signal indicates that the sample is homozygous (Fig. 3 (homozygous CC genotype)). The difference in curve shape and time at which the fluorescent signal crossed the threshold line allows for reliable determination of the genotype for each sample. Therefore, based on the results of amplification curve analysis, we obtained all variants (CC, TC, and TT) for IFNL4 (SNP rs12979860).

Analyses were conducted for the total sample of patients with HK and subgroups with primary HK and recurrent HK, and the results were compared with the control population group. Table 1 shows the distribution of genotype and allele frequencies for rs12979860 in the study group and population control group.

Fisher exact test showed a significant difference ($p = 0.0119 < 0.05$) in the distribution of genotypes and alleles between the study group (n = 50) and population control group (n=100). The homozygous (CC) genotype of rs12979860 was significantly more common in patients with HK (OR, 2.432; 95% CI, 1.213–4.957). Additionally, the CC genotype was significantly more common in patients with recurrent HK than in the population control group ($p = 0.03078$; OR, 2.423; 95% CI, 1.09–5.387).

We also compared the distribution of genotype and alleles for rs12979860 in the study group and the comparison group of women with a history of COVID-19 but without HK during hospitalization for COVID-19. The results of this comparison are presented in table 2.

Fisher exact test showed a significant difference ($p = 0.0007 < 0.05$) in the distribution of genotypes and allele frequencies between these two groups. The CC genotype of rs12979860 was significantly more common in patients with HK than in the comparison group (OR, 2.756; 95%

Table 1. Distribution of genotypes and polymorphic variants (alleles) in the IFNL4 gene in the examination group (1) versus primary keratitis (2) versus recurrent keratitis (3) versus the population control group

rs12979860 in the IFNL4 gene	1	2	3	4	P-value	OR (95% CI)
	Examination group, n=50	Primary HK, n=16	Recurrent HK, n=34	Control group, n=100		
Genotypes (%)						
TT	8.0%	0	12.0%	9.0%	P>0.05	-
TC	30.0%	37.0%	26.0%	51.0%	P>0.05	-
CC	62.0%	63.0%	62.0%	40.0%	P_{1-4}=0.0119	2.432 (1.213 – 4.957)
					P_{3-4}=0.03078	2.423 (1.09 - 5.387)
Alleles (%)						
T	23.0%	81.3%	75.0%	34.0%	P>0.05	-
C	77.0%	18.7%	25.0%	66.0%	P>0.05	-

Table 2. Distribution of genotypes and polymorphic variants (alleles) in the IFNL4 gene in the examination group (patients with herpetic keratitis) versus the comparison group

rs12979860 in the IFNL4 gene	Comparison group*, n=73	Examination group, n=50	P-value	OR (95% CI)
Genotypes, n(%)				
TT	18.0%	8.0%	P>0.05	-
TC	45.0%	30.0%	P>0.05	-
CC	37.0%	62.0%	0.007	2.756 (1.314 – 5.887)
Alleles				
T	40.0%	23.0%	P>0.05	-
C	60.0%	77.0%	P>0.05	-

* The group of patients with a history of COVID-19 and without signs of herpetic keratitis

Table 3. Distribution of genotypes and polymorphic variants (alleles) in the IFNL4 gene among patients with a history of mild COVID-19 infection and those with a history of moderate-to-severe COVID-19 infection in the examination group (patients with herpetic keratitis) versus the comparison group

rs12979860 in the IFNL4 gene	Examination group of patients with herpetic keratitis, n=50		Comparison group*, n=73		P-value	OR (95% CI)
	1	2	3	4		
	mild n=32	moderate-to-severe n=18	mild n=63	moderate-to-severe n=10		
Genotypes, n (%)						
TT	9.0%	5.0%	21.0%	0	P > 0.05	-
TC	31.0%	28.0%	46.0%	40.0%	P > 0.05	-
CC	60.0%	67.0%	33.0%	60.0%	P_{1-3} = 0.01772	2.923 (1.214 – 7.038)
Alleles						
T	25.0%	19.4%	43.7%	20.0%	P > 0.05	-
C	75.0%	80.6%	56.3%	80.0%	P > 0.05	-

* The group of patients with a history of COVID-19 and without signs of herpetic keratitis

CI, 1.314–5.887), which was similar to the comparison between the study group and the population control group.

The study group and the comparison group were subdivided into subgroups with a history of mild and moderate-to-severe COVID-19 infection. We compared the distribution of genotype and allele frequencies for rs12979860 between these groups (Table 3).

Fisher exact test showed a significant difference (p = 0.01772 <0.05) in the distribution of genotype CC between patients with both HK and a history of mild COVID-19 and the comparison group without signs of eye disease. The CC genotype was more common in patients with both HK and a history of mild COVID-19 than in individuals with a history of mild COVID-19 in the comparison group (OR, 2.923; 95% CI, 1.214–7.038).

Discussion

Although the exact mechanisms by which COVID-19 may trigger HSV-1 reactivation are not fully understood, several hypotheses have been proposed to explain this phenomenon. Patients with severe COVID-19 are known to exhibit reduced numbers of CD4+ and CD8+ T cells and NK cells in the blood. Patients with severe COVID-19 infection have impaired immunity characterized by a reduction in the number of CD4+and CD8+T cells; reactivation or coinfection with other viruses have been well-documented among COVID-19 patients [25].

Studies have found that SARS-CoV-2 infection is associated with a dysregulated immune response and may promote reactivation of latent viral infections (e.g., herpetic infection) [26, 27].

The individual's susceptibility to viruses is largely determined by genetic factors. A virus may cause a wide range of clinical presentations from asymptomatic to severe lesions. Several lines of evidence have been reported that indicate that such a difference is caused by human genetic variability: susceptibility to severe infection may be increased or decreased by the allelic variants of the genes that control the synthesis of immune system proteins [26].

The human body's immune reaction to SARS-CoV-2 infection involves innate and adaptive responses. An intracellular cascade signal leads to the production of numerous proinflammatory cytokines such as tumour necrosis factor (TNF), interleukin 1 (IL-1) and 6 (IL-6), and IFNs. IFNs typically protect the host from viral replication by inducing apoptosis of infected cells [28].

Studies on potential genetic factors of susceptibility to SARS-CoV-2 infection and sensitivity of various cells to this infection are promising for (i) identifying genetic markers for predicting the course of the disease and (ii) determining the fundamental basis for personalized therapy for COVID-19 [29].

The major genes under investigation are the Angiotensin-Converting Enzyme-2 (ACE2) receptor gene that affects entry of SARS COV-2 into cells; the ACE1 gene, which, along with the ACE2 gene, is a component of the renin-angiotensin system; and AB0 blood group genes [29, 30]. Our studies on ACE1 rs4646994 have found previously that carrying the I allele may be considered a potential risk factor for severe COVID-19 [31]. ACE1 gene expression was 20–30% lower in subjects carrying the ACE1 II genotype compared to those carrying the ACE1 ID genotype or DD genotype [32]. However, the ACE2 protein level in lung epithelial cells was increased in subjects carrying the ACE1 II genotype [33].

Several epigenetic phenomena (including epigenetic regulation of ACE2 and IL6) have been associated with SARS-CoV-2 infection. The change in IL6 expression has been associated with the development of worse COVID-19 symptoms due to excessive inflammation [34].

Toll-like receptors (e.g. TLT-4) and vitamin D receptor are important genetic factors in the regulation of expression of immune system genes and endothelial function genes (including renin-angiotensin system genes) [35].

Of note, an association of clinically significant retinal changes with ACE1 insertion-deletion genotypes in patients with various severity of COVID-19 has been found [36].

In our study on children affected by COVID-19, the C allele of rs12979860 was more common in children with recurrent respiratory infections compared to those with episodic viral infections ($p < 0.05$; OR 3.2; CI 1.52–6.71) [37]. That is, the allele C could be considered a risk allele for more frequent viral infections, which is likely to be associated with the stimulation of interferon-induced genes and increased production of pro-inflammatory cytokines [38]. In addition, we have found that the C allele could be considered a risk allele for pneumonia in pediatric patients with COVID-19 [37].

In the current study, we compared the distribution of genotype and allele frequencies for rs12979860 in the study group and the comparison group of adults with a history of COVID-19 but without HK during hospitalization for COVID-19. We found a statistically significant association between IFNL4 (SNP rs12979860) and susceptibility to HK in patients. The homozygous CC genotype was significantly more common among patients with HK than among individuals in the population control group and among patients with a history of COVID-19 but without ocular infection during hospitalization for COVID-19. Additionally, the CC genotype of rs12979860 was most frequent among patients with recurrent HK, which may indicate that it may serve as a potential marker of susceptibility to recurrent COVID-19.

Similar findings were reported by Borivoje et al (2019) [39] who aimed to investigate a potential association between the IL28B host genotype and recurrent HK. They found a significant association between recurrent HK and carrying the C allele of rs12979860 by homozygous CC individuals and heterozygous CT individuals. Moreover, findings of [39] are in agreement with those of our previous study on pediatric patients with COVID-19 [37] where the C allele of rs12979860 was more common in children with recurrent respiratory infections and those with pneumonia due to COVID-19.

In conclusion, we found an association between the homozygous CC genotype of IFNL4 (SNP rs12979860) with recurrent HK. The C allele could be viewed as a genetic marker of inherited predisposition to HK in individuals with a history of COVID-19.

Author Contributions

GID: Conceptualization and Study Design, Data Analysis and Interpretation, Writing – original draft, Writing – review & editing; KVS: Conceptualization and Study Design, Formal Analysis, Writing – original draft, LAL: Study Design, Formal Analysis, Writing – review & editing; OVG: Investigation, Formal Analysis, Writing – original draft; MVN: Investigation, Data Curation. All authors have read and approved the final manuscript and agree to be accountable for all aspects of the work.

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Conflict of interest

The authors declare no conflict of interest that could influence their views on the subject matter or materials described and discussed in this manuscript.

Disclaimer

This manuscript reflects the views of the authors and may not reflect the views of their institution or sponsor.

Ethical Approval

This study was approved by the Ethics committee of SI “The Filatov Institute of Eye Diseases and Tissue Therapy of the National Academy of Medical Sciences of Ukraine” (committee meeting minutes of September 8, 2025) and

Informed Consent

Written informed consent was obtained from all study subjects.

Data Availability Declaration

All the data obtained or examined during this study has been incorporated into this published article.

Abbreviations

FAM, fluorescein amidite (a fluorescent dye); HK, herpetic keratitis; HSV1, herpes simplex virus type 1; PCR, polymerase chain reaction; TAMRA, tetramethylrhodamine (a xanthene dye); VIC, an asymmetric xanthene dye.

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