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EFFECT OF GENETICS POLYMORPHISMS ON REINFECTION WITH COVID-19 AND PROGRESSION SEVERITY

Assiya A. Yessenbayeva[1]*, Meruyert R. Massabayeva[1], Bakytbek A. Apsalikov[1], Zaure S. Zholambayeva[1], Meruyert O. Khamitova[2], Zaituna G. Khamidullina[2], Laura T. Kassym[2]

[1] NCJSC "Semey Medical University", Semey, Republic of Kazakhstan;
[2] NCJSC "Astana Medical University", Astana, Republic of Kazakhstan.

Abstract

Relevance: In January 2020, the World Health Organization (WHO) announced the spread of a new coronavirus infection, COVID-19. The clinical picture of COVID-19 is wide, ranging from asymptomatic infection to acute respiratory distress syndrome, most often ending in death. Some viral infections are known to be followed by lifelong immunity, while others can lead to repeated infections throughout life. There is an urgent need to better understand whether those who have had COVID-19 are protected from reinfection or not.

The aim. In the present study, we examined the association of *IL2, IL6*, and *IL10* gene polymorphisms with COVID-19 reinfection and its severity in two cases of the disease.

Materials and methods: A total of 301 patients with a confirmed diagnosis of COVID-19 took part in a retrospective study, of which 76 patients had a second illness. Genetic research was carried out by real-time PCR.

Results: Of the 22 initially severe patients, 7 had re-developed COVID-19 in a severe form and 15 in a mild form. Of the 54 patients who first became ill with COVID-19 in a mild form, 16 re-developed a severe form of the disease and 38 re-developed a mild form. Results of the multifactorial inheritance model of *IL2* rs1801274, *IL6* rs2069840, *IL10* rs1800872 gene polymorphisms showed no statistically significant association with recurrent COVID-19 disease episode (p>0.2).

Conclusion. Polymorphisms of cytokine genes *IL2, IL6, IL10* are not associated with the severity of COVID-19 reinfection. Our results once again confirm the lack of long-term immunity after COVID-19 infection and the risk of reinfection, regardless of the severity of the first episode.

Keywords: *COVID-19, gene polymorphism IL2, IL6, IL10, reinfection.*

Резюме

ВЛИЯНИЕ ГЕНЕТИЧЕСКИХ ПОЛИМОРФИЗМОВ НА ПОВТОРНОЕ ЗАРАЖЕНИЕ COVID-19 И ТЯЖЕСТЬ ТЕЧЕНИЯ

Асия А. Есенбаева[1]*, Меруерт Р. Масабаева[1], Бакытбек А. Апсаликов[1], Зауре С. Жоламбаева[1], Меруерт О. Хамитова[2], Зайтуна Г. Хамидуллина[2], Лаура Т. Касым[2]

[1] НАО «Медицинский университет Семей», г. Семей, Республика Казахстан;
[2] НАО «Медицинский университет Астана», г. Астана, Республика Казахстан.

Введение. В январе 2020 года Всемирная организация здравоохранения (ВОЗ) объявила о распространении новой коронавирусной инфекции COVID-19. Клиническая картина при COVID-19 широка: от бессимптомной формы инфекции до острого респираторного дистресс-синдрома, наиболее часто заканчивающегося летальным исходом. Как известно после одних перенесенных вирусных инфекции остается иммунитет на всю жизнь, а другие могут привести к повторным заражениям в течение всей жизни. Существует острая необходимость лучше понять, защищены ли те, кто болел COVID-19, от повторного заражения или нет.

Цель. В настоящем исследовании мы хотели изучить взаимосвязь полиморфизмов генов *IL2, IL6, IL10* с повторным заболеванием COVID-19 и тяжестью течения в двух эпизодах заболевания.

Материалы методы: всего в ретроспективном исследовании приняли участи 301 пациент с подтвержденным диагнозом COVID-19, из них 76 пациентов переболели повторно. Генетическое исследование проводилось методом ПЦР в реальном времени.

Результаты. Из 22 первично тяжелых пациента, повторно 7 человек перенесли COVID-19 в тяжелой степени и 15 в легкой. Из 54 пациентов, перенесших COVID-19 в первый раз, в легкой степени, 16 имели тяжелое течение болезни повторно и 38 человек повторно болели легко. Результаты мультипликативной модели наследования полиморфизмов генов *IL2* rs1801274, *IL6* rs2069840, *IL10* rs1800872 показали отсутствие статистически значимой ассоциации с повторным эпизодом заболевания COVID-19 (p > 0,2).

Вывод. Полиморфизмы генов цитокинов *IL2, IL6, IL10* не ассоциированы с тяжестью течения COVID-19 при реинфецировании. Наши результаты еще раз подтверждают, что после перенесенной инфекции COVID-19 не остается долгосрочного иммунитета и существует риск повторного заражения.

Ключевые слова: *COVID-19, полиморфизм генов IL2, IL6, IL10, повторное заболевание.*

Түйіндеме

ГЕНЕТИКАЛЫҚ ПОЛИМОРФИЗМДЕРДІҢ COVID-19 ҚАЙТА ЖҰҚТЫРУЫНА ЖӘНЕ АҒЫМНЫҢ АУЫРЛЫҒЫНА ӘСЕРІ

Асия А. Есенбаева[1]*, Меруерт Р. Масабаева[1], Бакытбек А. Апсаликов[1], Зауре С. Жоламбаева[1], Меруерт О. Хамитова[2], Зайтуна Г. Хамидуллина[2], Лаура Т. Касым[2]

[1] «Семей медицина университеті» КеАҚ, Семей қ., Қазақстан Республикасы;
[2] «Астана медицина университеті» КеАҚ, Астана қ., Қазақстан Республикасы.

Кіріспе. 2020 жылдың қаңтарында Дүниежүзілік денсаулық сақтау ұйымы (ДДҰ) жаңа COVID-19 коронавирустық инфекциясының таралғанын жариялады. COVID-19-дың клиникалық көрінісі ауқымды: инфекцияның симптомсыз түрінен жедел респираторлық дистресс синдромына дейін, көп жағдайда өліммен аяқталады. Кейбір вирустық инфекциялардан кейін өмір бойы тұрақты иммунитет сақталады, кей инфекцияларды өмірінде бірнеше рет қайта жұқтыру қаупі бар. COVID-19-бен ауырғандардың қайта жұқтырылу қаупінің бар не жоқ болуын білу өте маңызды.

Мақсаты. Бұл зерттеуде біз *IL2, IL6, IL10* гендерінің полиморфизмдерінің COVID-19 бен қайта жұқтырылудың, аурудың екі эпизодындағы ауырлық ағымының байланысын зерттегіміз келді.

Материалдар мен әдістер: Ретроспективті зерттеуге COVID-19 диагнозы расталған барлық 301 пациент қатысты, олардың 76-сы қайта ауырды. Генетикалық зерттеу ПТР әдісімен нақты уақытта жүргізілді.

Нәтижелері: Бастапқы COVID-19 бен ауырған 22 ауыр науқастардың 7-і ауыр дәрежеде, 15-сі жеңіл дәрежеде ауруды басынан өткізді. COVID-19 бен ауырған 54 жеңіл дәрежелі науқастардың қайта ауырған кезде 16-да аурудың ауыр ағымы және 38- де жеңіл өтті.

IL2 rs1801274, *IL6* rs2069840, *IL10* rs1800872 гендерінің полиморфизмдерінің мультипликативті тұқым қуалау моделінің нәтижелері COVID-19 ауруының қайталанған эпизодымен статистикалық маңызды ассоциацияның жоқтығын көрсетті ($p > 0,2$).

Қорытынды. Реинфекциялану кезінде COVID-19 ағымының ауырлығы және *IL2, IL6, IL10* цитокин гендерінің полиморфизмдері байланысты емес. Біздің нәтижелер COVID-19 инфекциясынан кейін ұзақ мерзімді иммунитет сақталмайтынын және қайта жұқтыру қаупі бар екендігін тағы да растайды.

Түйін сөздер: *COVID-19, IL2, IL6, IL10 гендерінің полиморфизмі, қайталанатын ауру.*

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Introduction

In January 2020, the World Health Organization (WHO) announced the spread of a new coronavirus infection, COVID-19, which has since infected more than 607 million people worldwide and caused more than 6.51 million deaths. The clinical picture of COVID-19 is wide, ranging from asymptomatic infection to acute respiratory distress syndrome, most often ending in death. Age, gender, and comorbidities have an important influence on the severity and outcome of COVID-19 [11,16,35,25,33]. COVID-19 carries a high burden of mortality and morbidity. Some viral infections are known to be followed by lifelong immunity, while others can lead to repeated infections throughout life. It depends on the virus that leads to systemic infection with viremia, which creates long-term antibody responses, thereby protecting against infection for decades or more [27,2,12]. Viruses that do not have a viremic phase infect only the superficial mucosal layer and usually result in an antibody response that is detectable within a few months or a few years. Patients were thought to develop immunity after experiencing COVID-19, as with most acute respiratory viral diseases. As children, those who recover

from infections such as measles, chickenpox or mumps are protected for life [2]. In viruses such as influenza, acquired immunity depends on the strain and requires annual vaccination [13,7]. According to a study by many authors, patients who recovered from COVID-19 were found to have antibodies to SARS-CoV-2 in their tests [22,30,31,34,37]. In 90% of SARS-Cov-2 infections, antibodies begin to be produced about a week after the onset of symptoms, which persist for less than three months [32,17]. There is an urgent need to better understand whether those who have had COVID-19 are protected from reinfection or not. In comparison, some patients have been found to have very low levels of neutralizing antibodies, which increases the likelihood of reinfection with SARS-CoV-2. Reinfection and possible hospitalization is a major and costly public health problem in a pandemic [15,28]. "Reinfection" means that a person was infected with the pathogen, fully recovered, and then reinfected. Most reinfected patients with COVID-19 had a mild form that recovered [1,6,8] but one study reported hospitalization for reinfection (about 12%) [26]. Patients who were re-hospitalized had comorbidities, among which hypertension, diabetes, chronic kidney disease, coronary heart disease, hyperlipidemia, and obesity predominated [28,18,4] The severity of disease progression may depend on the patient's health status, demographics, and immune system development [5,9].

Some studies have found that patients with severe COVID-19 have higher levels of IL-2, IL-6, IL-7, IL-10, IP-10, MCP-1, TNF-α, macrophage inflammatory protein 1 alpha and CSF granulocytes than in patients with mild to moderate infections [19,10,24].

Serum cytokine levels that are elevated in Covid-19 patients have been associated with cytokine storm [14,20,39]. It has been reported that peripheral immune cells, cytokines, and their receptor expressions play an important role in patients suffering from critical pneumonia in COVID-19 [36]. IL-6 is one of the key cytokines contributing to host defense by stimulating acute phase reactions, hematopoiesis, and immune responses [21]. Serum IL-6 levels usually increase during infection, and a critical increase is observed in severe disease [29]. There is an increase in serum concentrations of pro- and anti-inflammatory cytokines (IL-2R, IL-6, TNF-α, and IL-10) in severe disease compared to moderate, mild, and asymptomatic [36]. Yang et al. studied 48 cytokines in patients with COVID-19, 14 of which were markedly elevated [38]. Among these 14 cytokines, IL-1, IL - 6, IL - 10 and MCP-3 have been identified as biomarkers of disease severity and mortality. They also found that IL-10 levels were markedly higher in patients with severe disease compared with mild COVID-19. Cytokines play an important role in the immune response of the body in response to the persistence of the virus, and polymorphisms of cytokine genes affect the overall expression and secretion of cytokines [23]. An analysis of the pathogenetic aspects of the development of severe forms of COVID-19 showed that cytokines are the most important mediators involved in the described processes.

Thus, some pro- and anti-inflammatory cytokines affect the severity of COVID-19, and we suggest that polymorphisms of the IL2, IL6, IL10 genes can be predictors of the severity of COVID-19 both in the first episode of the disease and during re-infection with COVID-19.

The aim. To study the association of *IL2, IL6, IL10* genes polymorphisms with the severity of COVID-19 both in the first episode of the disease and in case of re-infection with COVID-19.

Materials and Methods. In total 301 patients diagnosed with COVID-19 participated in the retrospective study. The selected patients were monitored using the Integrated Medical Information System program, with the written consent of the patients. Thus, we could know about the recurrence of COVID-19. Of the 301 initially ill patients, 76 patients had a second illness, the interval between the first and second episodes of the disease was more than 90 days, a twice positive PCR test from the nasopharynx for SARS-CoV-2 during the first and second episodes of the disease.

Of the total sample, 76 people had COVID-19 again. Of these, 22 had a severe progression (lung involvement more than 50%, SpO2<90, respiratory rate>30/min) and 54 mild progression of the disease (no lung involvement and clinical symptoms of the disease, SpO2>95%) at primary infection. Of the 22 initially severe patients, 7 people were reinfected with COVID-19 in a severe form and 15 in a mild one. Of the 54 patients who experienced mild COVID-19 for the first time, 16 had a severe progression of the disease again and 38 people had a mild illness again (Table 1). When comparing the two groups by sex and age, no statistically significant difference was found. The age of patients with mild and severe COVID -19 was 40 years with a standard deviation of 12.1 years, in the control group, the average age was 37 years, standard deviation of 12.3 ($p = 0.06$). It should be noted that the comparison of the main and control groups by gender also did not reveal a statistically significant difference ($p = 0.5$). (Table 1)

The study meets the requirements of the Declaration of Helsinki, the World Medical Association and was approved by the ethics committee of NC JSC “Semey Medical University”, Protocol No. 2 dated October 28, 2020. All participants in the study were informed about the objectives of the study and the upcoming procedures; all signed informed written consent to participate in the study.

DNA extraction was performed using QIAamp DNA MiniKit kits (QIAGEN, Germany), DNA concentration was measured using NanoDrop 1000 (ThermoScientific, Waltham, MA, USA). Prepared DNA was frozen and stored at -20°C. Genotyping was performed using CFX96™ Real-Time PCR (Bio-Rad) using primers and TaqMan probes. 40 ng of genomic DNA and 20 µl of TaqMan Genotyping MasterMix in 96-well plates (reagents manufactured by Life Technologies).

For a retrospective associated case-control study, comparing the frequencies of genotypic distributions between the study and control groups, the $\chi 2$ test was used. To describe the ratio of frequencies of genotypes and alleles of genes, the Hardy–Weinberg equilibrium was used. Differences between samples were considered statistically significant at $p<0.05$. Statistical analysis was performed using SPSS version 20 (IBMCorp.) and SNP Statversion 2.2.1. All variables were tested for normal distribution using the Shapiro-Wilk test. The odds ratio (OR) with 95%

confidence interval was calculated using logistic regression to estimate the effects of these differences.

Results

A total of 301 patients diagnosed with COVID-19 took part in the study. When comparing the two groups by sex and age, no statistically significant difference was found. The age of patients with mild and severe COVID-19 was 40 years with a standard deviation of 12.1 years, in the control group, the average age was 37 years, standard deviation of 12.3 (p = 0.06). It should be noted that the comparison of the two groups by gender also did not reveal a statistically significant difference (p = 0.5) (Table 1).

Table 1.

Distribution of the main and control groups by sex and age.

Primarily recovered from COVID-19, (n = 301)	Severe degree, (n=142)	Mild degree, (n=159)	P
Totally were reinfected with COVID-19, (n=76) Severe Mild	22 7 15	54 16 38	
Gender (male/female), (n=301)	69/73	84/76	0.5
Age: interval middle	21–72 40(12.1)	19-69 37(12.3)	0.06

The aim of the study was to find out if there is a relationship between polymorphisms genes *IL2, IL6, IL10* with recurrent COVID-19 disease and severity in two episodes of the disease.

As shown in Table 2, in dominant inheritance model, we see that genotype G/G single nucleotide polymorphism of the *IL2 gene* is less common 62 (44.6%) in patients with severe COVID-19 than in patients with mild disease 64 (41.6%). Genotypes A/A and A/G - in the main group 77 (55.4%) are less common than in the comparison group 90 (58.4%). In the recessive model of inheritance, the G/GA/G genotypes in the main group are less common 124 (89.2%) than in patients with a mild progression of the disease 131 (85.1%). Genotype A/A in the main group 15 (10.8%) is less common than in the comparison group 23 (14.9%). (Table 2).

Table 2.

Dominant and recessive model of inheritance of genotypes of gene polymorphism *IL2, IL6, IL10.* Comparison of the main group and the control group.

Model	Genotype	Main group	Control group	OR (95% CI)	P
IL2 rs(1801274)					
Codominant	G/G	62 (44.6%)	64 (41.6%)	1.00	0.55
	A/G	62 (44.6%)	67 (43.5%)	1.03 (0.62-1.71)	
	A/A	15 (10.8%)	23 (14.9%)	1.50 (0.71-3.19)	
Dominant	G/G	62 (44.6%)	64 (41.6%)	1.00	0.63
	A/GA/A	77 (55.4%)	90 (58.4%)	1.12 (0.70-1.81)	
Recessive	G/GA/G	124 (89.2%)	131 (85.1%)	1.00	0.28
	A/A	15 (10.8%)	23 (14.9%)	1.48 (0.73-3.00)	
Overly dominant	G/GA/A	77 (55.4%)	87 (56.5%)	1.00	0.79
	A/G	62 (44.6%)	67 (43.5%)	0.94 (0.58-1.51)	
Log addition	---	---	---	1.17 (0.83-1.65)	0.38

Table 3 shows in the dominant inheritance model that genotype G/G single nucleotide polymorphism of the *IL6 gene* is less common 72 (50.7%) in patients with severe COVID-19 than in patients with mild disease 84 (52.8%). Genotypes C/GC/C in the main group 70 (49.3%) are less common than in the comparison group 75 (47.2%). In the recessive model of inheritance, the G/GC/G genotypes in the main group are less common 126 (88.7%) than in patients with a mild progression of the disease 142 (89.3%). Genotype C/C in the main group 16 (11.3%) is less common than in the comparison group 17 (10.7%). (Table 3).

Table 3.

Dominant and recessive pattern of inheritance of genotypes of gene polymorphism *IL6.* Comparison of the main group and the control group.

Model	Genotype	Main group	Control group	OR (95% CI)	P
IL6rs(2069840)					
Codominant	G/G	72 (50.7%)	84 (52.8%)	1.00	0.75
	C/G	54 (38%)	58 (36.5%)	0.86 (0.52-1.42)	
	C/C	16 (11.3%)	17 (10.7%)	1.13 (0.53-2.43)	
Dominant	G/G	72 (50.7%)	84 (52.8%)	1.00	0.72
	C/GC/C	70 (49.3%)	75 (47.2%)	0.92 (0.58-1.46)	
Recessive	G/GC/G	126 (88.7%)	142 (89.3%)	1.00	0.63
	C/C	16 (11.3%)	17 (10.7%)	1.20 (0.57-2.51)	
Overly dominant	G/GC/C	88 (62%)	101 (63.5%)	1.00	0.49
	C/G	54 (38%)	58 (36.5%)	0.84 (0.52-1.37)	
Log addition	---	---	---	0.99 (0.71-1.40)	0.97

Table 4 shows the results of the dominant and recessive patterns of inheritance of gene polymorphism genotypes *IL10.* Genotype G/G single nucleotide polymorphism of the *IL10 gene* is less common 61 (44.5%) in patients with severe COVID-19 than in patients with mild disease 64 (41.6%). Genotypes A/A and A/G - in the main group 76 (55.5%) are less common than in the comparison group 90 (58.4%). In a recessive inheritance pattern, G/GA/G genotypes are less common in patients with severe COVID-19 122 (89%) than in patients with mild disease 131 (85.1%). Genotype A/A in the main group 15 (10.9%) is less common than in the comparison group 23 (14.9%). (Table 4)

Table 4.

Dominant and recessive pattern of inheritance of genotypes of gene polymorphism *IL10.* Comparison of the main group and the control group.

Model	Genotype	Main group	Control group	OR (95% CI)	P
IL10 rs(1800872)					
Codominant	G/G	61 (44.5%)	64 (41.6%)	1.00	0.58
	A/G	61 (44.5%)	67 (43.5%)	1.03 (0.62-1.71)	
	A/A	15 (10.9%)	23 (14.9%)	1.48 (0.69-3.15)	
Dominant	G/G	61 (44.5%)	64 (41.6%)	1.00	0.64
	A/GA/A	76 (55.5%)	90 (58.4%)	1.12 (0.69-1.80)	
Recessive	G/GA/G	122 (89%)	131 (85.1%)	1.00	0.3
	A/A	15 (10.9%)	23 (14.9%)	1.45 (0.72-2.96)	
Overly dominant	G/GA/A	76 (55.5%)	87 (56.5%)	1.00	0.8
	A/G	61 (44.5%)	67 (43.5%)	0.94 (0.59-1.51)	
Log addition	---	---	---	1.16 (0.82-1.64)	0.4

Our results did not show statistically significant differences in the distribution of alleles and genotypes or different genetic patterns (dominant vs. recessive) between both patients with the first episode of the disease and with reinfection of COVID-19.

Discussion

COVID-19 reinfection has been reported worldwide and has been described by several authors [12]. The severity of disease progression can vary depending on the patient's health status, demographics, and immune system development. Previously, a meta-analysis by Arafkas et al. reported no cases of reinfection after COVID-19 [3]. However, cases of reinfection were observed in our study. Thus, of the 22 patients who had a severe COVID-19 in the primary episode, 7 had severe and 15 had mild disease, and of the 54 patients who had a mild COVID-19 for the first time, 16 had severe disease again and 38 had re-infection with mild disease. It should be noted that the majority of reinfected cases of COVID-19 were mild. However, there were patients in whom the disease was severe, both at the first episode and at reinfection.

In this study, we also evaluated the association of cytokine gene polymorphisms *IL2, IL6, IL10* with COVID-19 reinfection and its severity in two cases of the disease. Unfortunately, the results obtained do not confirm the association of *IL2* rs1801274, *IL6* rs2069840, and *IL10* rs1800872 polymorphisms with COVID-19 reinfection and its severity.

Conclusions. Our study once again confirms that there is no long-term immunity after COVID-19 infection and, consequently, there is a risk of reinfection after complete recovery. Cytokine gene polymorphisms *IL2* rs1801274, *IL6* rs2069840, *IL10* rs1800872 are not associated with the severity of COVID-19 reinfection.

Authors' contributions. *Author contribution statement: All authors were equally involved*

Conflict of Interest. *The authors declare that they have no competing interests.*

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Contact information:
Yessenbayeva Assiya - Department of General Medicine., NCJSC “Semey Medical University”, Semey, Republic of Kazakhstan.
Mailing Address: 103, Abaya street, Semey, 071400, Republic of Kazakhstan.
E-mail: assiya.yessenbayeva@smu.edu.kz
Mob.phone: 8 777 236 16 97