Received: 03 August 2021 / Accepted: 21 Desember 2021 / Published online: 28 February 2022

DOI 10.34689/SH.2022.24.1.005

УДК 575.174.015.3

INTERLEUKINS 10 AND 17A: THE RELATIONSHIP OF GENE POLYMORPHISMS TO DISEASE AND CYTOKINE LEVELS IN PATIENTS WITH BRUCELLOSIS IN THE KAZAKH POPULATION

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Abstract

Актуальность: In predicting the clinical course of brucellosis, the participation of a genetic factor, in particular, gene polymorphism of some cytokines, which are essential in the development of the disease, is not excluded. In this regard, the search for genetic markers of susceptibility and features of the course of the disease among the alleles of cytokine gene polymorphisms is of theoretical and practical interest.

Aim of research was to study the associations of the polymorphisms of the IL10 and IL17 genes with brucellosis, as well as their connection with the production of the same cytokines in patients with brucellosis of Kazakh nationality.

Materials and Methods. In the case-control study, there were 89 patients and 422 healthy individuals of the Kazakh population. Genotyping was performed by real-time PCR. The determination of cytokine levels in the blood plasma was carried out by enzyme immunoassay.

Results. It has been established that susceptibility factors for brucellosis can be C allele and CC genotype (OR=4.42 and 7.32; 95% CI: 3.0–6.51 and 4.39–12.20, respectively), and T allele, CT, and TT genotypes of the rs8193036 polymorphism are resistance factors. Relationship was found with susceptibility to brucellosis in carriers of the G allele and GG genotype of the rs2275913 polymorphism (OR=2.26 and 2.25; 95% CI: 1.51-3.38 and 1.40-3.61), and with resistance - A allele and genotypes AA and AG. The concentration of IL-17A in patients with brucellosis with CC, CT and GG genotypes was higher compared with the control group (p=0.054, 0.002 and 0.012, respectively).

Conclusions. Thus, IL17A gene polymorphisms can be associated with brucellosis disease, with the level of the cytokine itself in the Kazakh population.

Keywords: *brucellosis, gene polymorphism, interleukins, association, Kazakh population.*

Резюме

ИНТЕРЛЕЙКИНЫ 10 и 17А: СВЯЗЬ ПОЛИМОРФИЗМОВ ГЕНОВ С ЗАБОЛЕВАНИЕМ И УРОВНЕМ ЦИТОКИНОВ У БОЛЬНЫХ БРУЦЕЛЛЕЗОМ В КАЗАХСКОЙ ПОПУЛЯЦИИ

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Актуальность. В прогнозировании клинического течения бруцеллеза не исключается участие генетического фактора, в частности, полиморфизма генов некоторых цитокинов, имеющих существенное значение в развитии заболевания. В связи с этим поиск генетических маркеров восприимчивости и особенностей течения заболевания среди аллелей полиморфизмов генов цитокинов представляет теоретический и практический интерес.

Целью нашего исследования является изучение ассоциаций полиморфизмов генов *ИЛ10* и *ИЛ17* с бруцеллезом, а также их связи с продукцией одноименных цитокинов у больных бруцеллезом лиц казахской национальности.

Материалы и методы. В исследовании случай-контроль было 89 больных и 422 здоровых лиц казахской популяции. Набор материала проводился на базе Клинической инфекционной больницы г. Семей, Казахстан. Генотипирование выполнялось методом ПЦР в режиме реал-тайм. Определение уровней цитокинов в плазме крови проводилось методом иммуноферментного анализа. Для статистической обработки использовались критерий χ^2 Пирсона и отношение шансов (ОШ) с 95% доверительными интервалами (ДИ), критерии Краскела-Уоллеса и Манна-Уитни.

Результаты исследования: Установлено, что факторами предрасположенности к бруцеллезу могут быть С аллель и СС генотип (ОШ = 4,42 и 7,32; 95% ДИ: 3,0-6,51 и 4,39-12,20, соответственно), а Т аллель, СТ и ТТ

генотипы полиморфизма rs8193036- факторами резистентности. Выявлена связь с предрасположенностью к бруцеллезу у носителей Gаллеля и GG генотипа полиморфизма rs2275913 (ОШ = 2,26 и 2,25; 95% ДИ: 1,51-3,38 и 1,40-3,61), а с резистентностью - А аллеля и генотипов АА и AG. Концентрация ИЛ-17 А у больных бруцеллезом с СС, СТ и GG генотипами была выше по сравнению с контрольной группой (p = 0,054, 0,002 и 0,012, соответственно). У больных с генотипами АА и GA уровень ИЛ-10 был ниже по сравнению с лицами контрольной группы (p<0,001 и p<0,001, соответственно).

Выводы: Таким образом, полиморфизмы гена *ИЛ17А* могут быть связаны с заболеванием бруцеллезом, с уровнем самого цитокина, а полиморфизм гена *ИЛ10* с уровнем ИЛ-10 у больных бруцеллезом в казахской популяции.

Ключевые слова: *бруцеллез, полиморфизм генов, интерлейкины, ассоциация, казахская популяция.*

Түйіндеме

10 ЖӘНЕ 17А ИНТЕРЛЕЙКИНДЕРІ: ҚАЗАҚ ПОПУЛЯЦИЯСЫНДА ГЕН ПОЛИМОРФИЗМДЕРІНІҢ БРУЦЕЛЛЕЗ АУРУЫМЕН ЖӘНЕ ЦИТОКИНДЕР ДЕҢГЕЙІМЕН БАЙЛАНЫСЫ

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Өзектілігі. Бруцеллездің клиникалық ағымын болжамдау кезінде аурудың пайда болуында маңызы бар генетикалық фактордың (кейбір цитокиндердің полиморфизмдері) қатысуы жоққа шығарылмайды. Сондықтан, ауруға бейімділік пен оның ағымының ерекшеліктерінің генетикалық маркерларын іздеу теоретикалық және практикалық қызығушылық тудырады.

Зерттеудің мақсаты: Бруцеллезбен ауыратын қазақ науқастарында ИЛ10 және ИЛ17 гендік полиморфизмдерінің бруцеллез ауруымен және осы цитокиндердің деңгейімен байланысын анықтау.

Құралдар мен әдістер. Зерттеуде 89 науқас және 422 сау қазақ қатысты. Науқастардан материалдар Семей қаласының Жұқпалы аурулар ауруханасында жиналды. Набор материала проводился на базе Клинической инфекционной больницы г. Семей, Казахстан. Генотиптеу нақты уақыт режимінде полимеразды тізбекті реакция әдісімен жасалды. Плазмадағы цитокиндер деңгейі иммуноферменттік сараптама әдісімен анықталды. Определение уровней цитокинов в плазме крови проводилось методом иммуноферментного анализа. Статистикалық өңдеу χ^2 Пирсон критериін және 95% сенімді интервалымен (СИ) шанстар қатынасын (ШҚ), Краскел-Уоллес және Манна-Уитни критерийлерін қолданумен жүргізілді.

Зерттеудің нәтижелері: rs8193036 полиморфизмінің С аллель және СС генотип (ШҚ = 4,42 және 7,32; 95% СИ: 3,0-6,51 және 4,39-12,20, сәйкес) бруцеллезге бейімділік факторлары болып, Т аллель, СТ және ТТ генотиптері аурудан қорғайтын факторлары болуы мүмкін. Бруцеллезге бейімділікпен rs2275913 полиморфизмінің Gаллель және GG генотип (ШҚ = 2,26 және 2,25; 95% СИ: 1,51-3,38 және 1,40-3,61) тасымалдаушыларында, ал резистенттілікпен А аллель және АА, AG генотип тасымалдаушыларында байланыс анықталды. ИЛ-17 А деңгейі бруцеллезбен ауыратын науқастарда СС, СТ және GG генотиптерімен сау адамдарға қарағанда жоғары болды (p = 0,054, 0,002 және 0,012). АА және GA генотиптерімен науқастарда ИЛ-10 деңгейі сау адамдарға қарағанда төмен болды (p<0,001 және p<0,001).

Қортынды: Сонымен, *ИЛ17А генінің полиморфизмдері бруцеллез ауруымен және цитокин деңгейімен, ал ИЛ10 гендік полиморфизмі* ИЛ-10 деңгейімен бруцеллезбен ауыратын қазақ науқастарда байланысты болуы мүмкін.

Түйінді сөздер: *бруцеллез, гендік полиморфизм, интерлейкиндер, байланыс, қазақ популяциясы.*

Bibliographic citation:

Mukovozova L.A., Bekenova N.B., Tokayeva A.Z., Kassym L.T., Smail E.M. Interleukins 10 and 17A: the relationship of gene polymorphisms to disease and cytokine levels in patients with brucellosis in the Kazakh population // Nauka i Zdravookhranenie [Science & Healthcare]. 2022, (Vol.24) 1, pp. 39-46. doi 10.34689/SH.2022.24.1.005

Муковозова Л.А., Бекенова Н.Б., Токаева А.З., Касым Л.Т, Смаил Е.М. Интерлейкины 10 и 17А: связь полиморфизмов генов с заболеванием и уровнем цитокинов у больных бруцеллезом в казахской популяции// Наука и Здравоохранение. 2022. 1(Т.24). С. 39-46. doi 10.34689/SH.2022.24.1.005

Муковозова Л.А., Бекенова Н.Б., Токаева А.З., Қасым Л.Т, Смаил Е.М. **10 ж**әне 17А интерлейкиндері: қазақ популяциясында ген полиморфизмдерінің бруцеллез ауруымен және цитокиндер деңгейімен байланысы // Ғылым және Денсаулық сақтау. 2022. 1 (Т.24). Б. 39-46. doi 10.34689/SH.2022.24.1.005

Introduction. Brucellosis belongs to the number of zoonoses that represents the most important problem for many countries, including the Republic of Kazakhstan. The urgency and socio-economic significance of this infection is determined not only by the high incidence of disease, but also by a high percentage of the chronicity of the infection process (40-50%) and disability of patients (up to 13% and above) [22, 38].

The individual susceptibility of the organism to infections depends on the pathogenicity of the microorganism, the condition of the body's immune system and environmental factors [31]. Differences in genes controlling the defense reactions of the organism, which also include cytokine genes, can cause a different nature of the inflammatory response and specific immunological responses when introducing pathogens. The most frequent change in the structure of cytokine genes is single nucleotide polymorphism (SNP) [29, 31].

It is believed that it is the single-point mutations due to the formation of specific alleles of genes that cause phenotypic differences between people, including individual development features of protective reactions, as well as a predisposition to a number of diseases [29].

The importance of studying polymorphisms of cytokine genes is due not only to the fact that they can serve as markers of predisposition and resistance to the disease, but also their effect on the level of protein production (cytokine). Imbalance of cytokines, associated with the hyper production of some of them and the hypo production of others, plays a very important role in the progress and outcome of any infectious disease.

Currently, there are a significant number of studies in the literature in which associations between variants of alleles of regulatory molecule genes and predisposition to various diseases, including infectious ones, have been revealed.

Thus, in vitro, polymorphism gene of the IL10 at position -1082 G / A (rs1800896) plays an important role in infectious diseases, as it is associated with the level of the cytokine itself [28]. Besides, it can affect the balance of cytokines of T helpers type 1 and T helpers type 2 (Th1 / Th2) and thereby affect the sensitivity to infectious diseases and their outcomes [21]. According to some authors [1, 2, 9, 28, 35], the G allele is associated with IL-10 production at higher concentrations, while the A allele is associated with a low level of this cytokine [25, 35].

According to the meta-analysis, the AA polymorphism genotype IL10 -1082 GA (rs1800896) was associated with a significantly lower risk of infection with the hepatitis B virus in the Chinese population [39]. However, it is assumed that the polymorphisms of the IL10 gene increase the risk of developing hepatocellular carcinoma among Korean, Taiwanese and Chinese populations.

Afzal M. et al. [1], based on their studies conducted in Pakistan, suggest that the GG carriers of a genotype have a predisposition to chronic viral hepatitis C higher than those of carriers of other genotypes. Similar conclusions that the GG genotype of polymorphism -1082 G / A is associated with chronic viral hepatitis C were made by other scientists [9]. According to these authors [9], this genotype also determines the increased production of IL-10. At the same time, according to a number of authors [1, 11], the carriage of the heterozygous variant of GA was associated with resistance to chronic viral hepatitis B, as well as spontaneous elimination of the hepatitis virus C, showing the protective role of this genotype in this infection [11].

As for the bacterial infections, the results of research available in the literature now in this direction are few and contradictory. Thus, a significant association of AA genotype polymorphism of the IL10 gene in the position -1082 G / A with tuberculosis was revealed in studies conducted among the Chinese population. At the same time, other authors [20] in their studies suggest that the risk of tuberculosis was associated with a GA genotype. Authors [20] found statistically significant differences in the GG genotype in patients with tuberculosis with individuals in the controlled group. The GG genotype was more common in healthy individuals. In contrast to these findings, studies conducted in children in Egypt did not reveal a significant relationship between this polymorphism with the tuberculosis infection [21].

In our studies performed in the erysipelas infected individuals of the Kazakh population, there was no statistically significant association between the polymorphism of the IL-10 gene-1082 GA (rs1800896) and the erysipelas, irrespective of the nature of the disease course [4].

As for the association of the polymorphism of IL-10 gene-1082 GA (rs1800896) with brucellosis, there are very contradictory opinions in the literature.

The results of the study of the polymorphism of IL-10 (-1082 G / A) in the studies of *Kazemi S. et al.* showed that the GG genotype can be considered as a risk factor for brucellosis, while the AG genotype can be a factor of resistance to the disease [16]. Similar conclusions were made in a study conducted among the Turkish population. The authors believe that this polymorphism can affect susceptibility to brucellosis and increases the risk of developing the disease [8]. Although, in studies of Karaoglan I. et al. were not found significant differences between the allele frequency and the distribution of the genotypes of the IL10 polymorphisms (-1082) between patients and the control group [15]. Another study indicates the absence of a link between the polymorphism of the IL10 gene and brucellosis, as well as with complicated course [7].

The interleukin gene -17A (IL17A) consists of 3 exons (2 introns) and is localized on the 6 chromosomes: 6p12.2. The most studied two polymorphisms of this gene are rs2275913 and rs8193036 located in the 5'-protein-coding region [http://www.ncbi.nlm.nih.gov/gene/3605].

It is suggested that the T allele of the rs8193036 polymorphism in the 5'-protein coding region is associated with a decrease in the transcriptional activity of the IL-17A gene [14]. Low transcriptional activity, in turn, may be the cause of delayed protein synthesis, in this case, IL-17A. At the same time, in our previous studies it was found that the polymorphism of rs8193036 of the IL-17A gene, in particular the CC genotype, can be associated with hyper production of IL-17A [5].

Polymorphism gene of IL-17A rs2275913 may be associated with the risk of developing hepatocellular carcinoma in chronic viral hepatitis B, by influencing on the production of the IL-17A itself. The authors suggest that the

GG genotype is associated with an increase of the level of IL-17A and Ig E level in viral hepatitis [18].

In addition, in studies conducted in patients with bronchial asthma in Saudi Arabia, a hypo production of IL-17A in carriers of the genotype CT of the polymorphism gene of IL-17A was detected [3]. In Kazakh patients with erysipelas, hyper production of IL-17A in carriers of GA genotype was also found [5]..

In our previous studies it was shown that the polymorphism rs2275913 of IL-17A can be associated with erysipelas among the people of Kazakh nationality [6].

Contradictory results were obtained by studying the polymorphism rs2275913 of the IL-17A gene in patients with tuberculosis. Significant associations of this polymorphism with a predisposition to pulmonary tuberculosis were established in the Spanish population [24], whereas among the Chinese population no such link was identified [10].

The role of cytokine IL-17A in the pathogenesis of brucellosis, some authors explain by its influence on the induction of an immune response mediated by Th1, which is necessary to control brucella. It is also assumed that the balance of cytokines Th1 / Th2 may be involved in the processes of resistance or susceptibility to brucellosis: Th1 cytokines provide resistance, whereas Th2 cytokines predispose to brucellosis [27].

The AA genotype of the IL17A gene polymorphisms (rs4711998, rs8193038, rs3748067) according to Rasouli M. et al, are considered as susceptibility factors to brucellosis, while GG and AA genotypes of rs3819025 and rs3819025 polymorphisms as resistance factors, respectively [27].

It should be noted that the results of most studies indicate the presence of associations between polymorphisms of cytokine genes and predisposition / resistance to various infectious diseases, but they differ significantly in different populations.

Until now, there is no information in the literature related to the study of polymorphisms of the IL10 and IL17A genes and their connection with the production of these cytokines in patients with brucellosis of Kazakh population.

Consequently, **the purpose of our study** is to study the associations of polymorphisms of IL10 and IL17 genes with brucellosis, as well as their connection with the production of the same cytokines in patients with brucellosis of Kazakh people.

Materials and methods

The total number of involved patients with brucellosis was 89 people. Of these, 80 patients from 89 were genotyped by polymorphism rs1800896 of the IL10 gene, polymorphism rs8193036 of the IL17A-83 gene, and polymorphism rs2275913 of the IL17A gene-89 patients with brucellosis. The design of the study is "case-control" [13]. Selection in the group of cases diagnosed with brucellosis was carried out by a continuous method from the patients admitted to the hospital of infectious diseases in Semey (Kazakhstan), consistently for the period from 2015 to 2017. In addition, a number of patients were admitted in the family-doctor outpatient clinics and clinics in Semey. The control group was formed from the persons who underwent prophylactic examinations in the same family-doctor outpatient clinics and clinics. The number of patients studied in the control group was 422 in total, of which 422 people of control group were genotyped by the polymorphism rs1800896 of the IL10 gene, and 414 by the polymorphisms of the IL17A gene (rs8193036, rs2275913).

The levels of IL-10 and IL-17A were identified in patients and persons in the control group who were genotyped. Of the 422 persons included in the control group, the levels of IL-10 and IL-17A were randomly selected to achieve an equal number of participants (89 persons). However, in 1 patient out of 89 due to failure, the level of IL-17A and IL-10 was not determined.

The criteria for inclusion in the group of cases were: a determined diagnosis of brucellosis, age of 18 years and older, Kazakh nationality, residence in the city of Semey. The criteria for exclusion were genetic diseases in anamnesis, oncological diseases, chronic viral hepatitis, immunodeficiency in the anamnesis, kidney disease, cardiovascular system, liver, end-stage blood and other diseases that can affect the level of cytokines IL-17A and IL- 10.

The inclusion criteria for the control group were: the excluded diagnosis of brucellosis and the absence of a history of disease, age 18 and over, Kazakh nationality, residence in the city of Semey. The exclusion criteria were similar to those in the group of cases.

All participants in the study were genotyped using the polymorphisms rs1800896 of the gene IL10, rs8193036 and rs2275913 of the IL-17A gene. Isolation of genomic DNA from the blood was performed using QIAamp DNA Mini Kit (QIAGEN, Germany) in accordance with the manufacturer's instructions. The DNA concentrations were measured with a help of Nanophotometer P330 (Implen). DNA genotyping was carried out on the CFX96 ™ Real-Time PCR (Bio-Rad) amplifier. The amplification program included preliminary denaturation at 94 °C for 3 minutes, then 50 cycles at 94 °C for 10 seconds and at 58 °C for 50 seconds. The research was carried out on the basis of the Republican State Enterprise (RGP) "National Center for Biotechnology", Astana, Republic of Kazakhstan.

The level of IL-17A and IL-10 was determined by the method of enzyme immunoassay using commercial test systems Vector-Best (Novosibirsk, Russia) [23] on the basis of the Joint Research Laboratories of the Semey Medical University. For this purpose, patients with brucellosis were collected blood in a volume of 5 ml in tubes with EDTA (ethylenediaminetetraacetate).

Statistical processing of data

A comparison of the frequency of occurrence of genotypes between a group of cases and a control group was carried out using the Pearson $\chi 2$ criterion and odds ratio (OR) with 95% of confidence intervals (CI) [12]. The ratio of frequencies of genotypes and allelic variants of genes was checked for compliance with the Hardy-Weinberg law. Statistical calculations were carried out on a calculator for genetic calculations under the Gene Expert program (http://gen-exp.ru/calculator_or.php).

The content of IL-17A and IL-10 in the blood plasma was analyzed using medians and quartiles (Me, Q1 and Q3, respectively). Considering the fact that the distribution of IL17A in plasma differed from normal, nonparametric criteria were used for intergroup comparisons [12, 33]. Next, we compared the levels of IL-10 and IL-17A within the same

genotype in patients with faces of control group. These group comparisons were performed using the Mann-Whitney test, and the differences were considered significant at p <0.05. The Data was processed using STATA 13 (Stata Corp. TX, USA) [34].

Ethical Compliance

The study protocol was developed and approved at the meeting of the Ethical Committee of the Semey Medical University (Kazakhstan) (Minutes No. 2 dated November 13, 2013). All participants of the study were informed of the purpose and methods of the study and gave their written consent for participation.

The results

Association of polymorphisms of cytokine genes IL17A and IL10 with brucellosis.

Genotyping by the polymorphism of the gene IL17A (rs8193036) made it possible to identify the presence of the link between alleles and genotypes of this polymorphism with brucellosis. As a result of our research, it has been determined that the factors of predisposition to brucellosis can be the C allele and the CC genotype, and the T allele, CT and TT genotypes of polymorphism rs8193036 of the IL17A gene are the factors of resistance. The data are presented in Table 1.

Table 1.

Association of polymorphism rs8193036 of the IL17A gene with brucellosis.

Comparedgroups	Allele/genotype	χ^2	p	OR (95% CI)
Patients with brucellosis (n=82) and persons of the control group (n=414)	C	63.19	0	4.42 (3,00 – 6,51)
	T			0.23 (0.15 – 0.33)
	CC	71.07	0	7.32 (4,39 – 12,20)
	CT			0.43 (0,26 – 0,72)
	TT			0.19 (0,09 – 0,43)

In our study, both cases (patients with brucellosis) and those people in the control group were in the Hardy-Weinberg equilibrium (p=0.11 and p=0.98).

Statistically significant associations with brucellosis, as a result of our study, have been identified with the polymorphism rs2275913 of the IL17A gene. The results of the study showed that there is a possible connection with a predisposition to brucellosis in carriers of the G allele and the GG genotype. Thus the protective factors can be presented with the carriage of the A allele and the genotypes AA and AG. The data are presented in Table 2.

Table 2.

Association of polymorphism rs2275913of the IL17A gene with brucellosis.

Comparedgroups	Allele/genotype	χ^2	p	OR (95% CI)
Patients with brucellosis (n=89) and persons of the control (n=414)	A	16,8	0,0001	0,44 (0,30 – 0,66)
	G			2,26 (1,51 – 3,38)
	AA	16,09	0,0003	0,08 (0,01 – 0,61)
	AG			0,69 (0,43 – 1,11)
	GG			2,25 (1,40 – 3,61)

Table 3.

Association of polymorphism rs1800896 of the IL10 gene with brucellosis.

Allele/genotype	χ^2	p	OR (95% CI)
A	0,70	0,4	1,17 (0,81 – 1,71)
G			0,85 (0.58 – 1.24)
AA	7.06	0.03	0.92 (0,57 – 1,49)
AG			1.54 (0,95 – 2,49)
GG			0.20 (0,05 – 0,86)

The results of our study on the association of polymorphism IL10 gene (rs1800896) with brucellosis disease have shown that the GG genotype can be the factor of resistance to brucellosis. However, the cases (patients with brucellosis) were not in the Hardy-Weinberg equilibrium in these samples (p=0.02). The Hardy-Weinberg test for the controls showed that the controls corresponded to the Hardy-Weinberg equilibrium (p=0.11). Data on the study results of the relationship of the genetic marker (IL10 (rs1800896) with the development of brucellosis are presented in Table 3.

Relationship between gene polymorphisms and cytokine levels.

When the IL-17A levels were compared within the same genotype, statistically significant differences of the IL-17A content were observed in the cases and people in the control group with the HS and CT genotypes. In patients with brucellosis, the level of IL-17A was higher in comparison with the control group people both in the carriers of the SS genotype and in the carriers of the CT genotype. The data are presented in Table 4.

Table 4.

Comparison of IL-17A levels in patients with brucellosis and control group, depending on genotypes.

Genotypes	Number of patients and persons of control group with genotype		Me	Q_1	Q_3	P
CC	cases	52	7,730	1,607	10,567	p=0,054
	control	12	2,965	1,618	5,003	
CT	cases	24	3,526	2,860	10,567	p=0,002
	control	46	3,519	0,600	6,749	
TT	cases	7	2,321	0,356	3,035	p=0,11
	control	30	5,276	2,175	6,860	

Statistically significant differences in the level of IL-17A between patients and healthy individuals within the same genotype were detected only in carriers of the genotype GA. In patients with brucellosis of GA genotype, hyper production of IL-17A was observed in comparison with those of the control group. The data are presented in Table 5.

Table 5.

Comparison of IL-17A levels in patients with brucellosis and control group, depending on genotypes.

Genotypes	Number of patients and persons of control group with genotype		Me	Q_1	Q_3	P
GG	cases	57	5,937	1,922	10,509	p=0,012
	control	39	5,000	0,600	6,671	
GA	cases	31	7,647	1,428	10,391	p=0,10
	control	34	4,352	1,993	6,860	
AA	cases	1*				p=0,875
	control	15	3,330	0,352	5,004	

Note: * The median, quartiles 1 and 3 in the carriers of AA genotype in patients with brucellosis not shown, because the level of IL-17A with this genotype is defined only in one case.

As for comparing the levels of IL-10 in patients with brucellosis and persons of the control group within the same genotype, the statistically significant differences in the content of IL-10 have been identified among the carriers of AA and GA heterozygous genotype. In patients with genotypes AA and GA level of IL-10 was lower compared with those in the control group carriers of the same genotype. The data are presented in Table 6.

Discussion

Thus, the results of our studies, brucellosis associated with allele C, CC genotype polymorphism rs8193036, allele G and GG genotype polymorphism rs2275913 IL17A gene as possible predisposition factors and allele T and PT, TT genotypes (rs8193036), the allele A and AA (rs2275913) polymorphism genotype IL17A gene are resistance-associated. Also IL17A levels are associated with the genotypes CC and CT (rs8193036), GG (rs2275913) polymorphism IL17A gene heterozygous GA.

So far, studies have been conducted, the results of which indicate the existence of a connection between polymorphism rs8193036 and other diseases. Thus, *Wang J. et al.* [36] in their studies have shown that the carriers of the CC genotype polymorphism rs8193036 of the IL17A gene increase the risk of developing bronchial asthma in children of the Taiwan population. *Stappers M. et al.* [32] believe that the polymorphism rs8193036 of the IL17A gene and the polymorphisms of the genes of other cytokines affect the predisposition to skin diseases of infectious genesis. At the same time, according to *Bekenova N. et al*. [5], the CC genotype of the polymorphism rs8193036 of the IL17A gene was less common in patients with erysipelas than in those of the control group. As a result of our study, we found that the CC genotype of polymorphism rs8193036 is more common in patients with brucellosis, which gives grounds to suggest that it may be a predisposition factor to the disease.

According to several authors, the polymorphism rs2275913 of the IL17A gene is associated with an increased risk of cancer. Of the 3 polymorphisms of the IL17A gene (rs2275913, rs3819025 and rs3748067) and 5 IL-17F (rs763780, rs7771511, rs12203582, rs9382084 and rs1266828), only rs2275913 was associated with a risk of developing breast cancer in women in the Chinese population [37]. In studies conducted in Iran, the polymorphism rs2275913 of the IL17A gene was associated with a risk of stomach cancer [26] (*Rafiei A. et al., 2013*).

Similarly to our studies, *Bekenova N. et al.* [6], it was found that in patients with erysipelas, the allele G and GG genotype of the polymorphism rs2275913 of the IL17A gene are more likely to be associated with predisposition to the erysipelas, whereas the allele A may be associated with resistance to this disease. According to the results of our study, the factor of resistance to brucellosis can also be AA genotype polymorphism rs2275913 of the IL17A gene.

Han R. et al. [14] suggest that the allele T of the polymorphism rs8193036 of the IL17A gene in the 5'-protein coding region is associated with a decrease in the transcriptional activity of the IL17A gene, which in turn can be the cause of delayed protein synthesis, in this case IL-17A. According to our data, the level of cytokine in patients with HS and CT polymorphism rs8193036 of the IL17A gene was higher in patients than in the people of the control group.

According to the literature, low production of IL-10 was associated with the presence of a homozygous AA genotype of polymorphism of the IL10 gene (rs1800896) in patients with tuberculosis and in people of the control group [19]. Similar results were also found in our study. In carriers of AA and GA among patients with brucellosis, hypo production of IL-10 was observed. However, the cases during genotyping of the IL10 gene (rs1800896) did not correspond to the Hardy – Weinberg equilibrium. In this regard, we cannot talk about the association of the level of a given cytokine with its polymorphism at the position –1082 GA. Also, in patients with bronchial asthma with the genotypes GG and GA of the polymorphism of the IL10 gene (rs1800896) [17] at position -1082 GA, no differences in the level of IL-10 were revealed (the authors do not describe the AA genotype).

The design of the study can be attributed to the shortcomings of our research, since systematic mistakes can play an essential role in case-control studies. Selection of a group of cases and a control group was conducted within the city of Semey (Kazakhstan). In this regard, we can not extrapolate our results to the entire Kazakhstani population. Also to the shortcomings of our study we refer a small sample size, which allows us to identify only relatively strong links. Nevertheless, even this sample size allowed us to reveal statistically significant differences.

However, for the first time we conducted a case-control study to determine the polymorphisms of the IL17A genes (rs8193036 and rs2275913), IL10 (rs1800896) in order to identify their associations with brucellosis, that is, for the first time an attempt was made to elucidate the role of the genetic factor in the development of brucellosis in persons of Kazakh nationality. Also, the merits of our study can be attributed to the fact that in this study we first estimated the relationship between interleukin levels (IL-17A and IL-10) with polymorphisms of the genes of these interleukins.

As a result of our study, we determined that polymorphisms of the IL17A (rs8193036 and rs2275913) gene are associated with brucellosis disease. We also revealed the relationship between genotypes polymorphisms of cytokine gene and immunological parameters of blood, in particular, with the production of cytokines themselves. Based on the results of our study, we can assume that carriers of different genotypes among patients with brucellosis and healthy individuals may have different concentrations of IL-17A. Unfortunately, we can not talk about the influence of genotypes on the level of cytokines and the development of the disease, due to the shortcomings of this study design (case-control). In this regard, further research is needed to determine the immuno-genetic mechanisms of the development of brucellosis.

Funding Source

Funds for research were provided by grant financing "Molecular genetic bases for predicting the outcomes of chronic viral hepatitis, erysipelas and brucellosis" (State registration number 0115RK 01852).

Authors' contributions: *Each of the authors made an equal contribution.*

Financing: *Funds for research were provided by grant financing "Molecular genetic bases for predicting the outcomes of chronic viral hepatitis, erysipelas and brucellosis" (State registration number 0115RK 01852).*

Conflicts of Interest: *The authors declare that they have no conflicts of interest.*

Publication details: *This material has not been published in other publications and is not pending review by other publishers.*

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