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Interregional differences in *IL-10* and *MMP2* gene polymorphisms in groups of patients with primary open-angle glaucoma in the Russian Federation according to a multicenter study

Konenkov V.I.[1], Shevchenko A.V.[1], Prokofiev V.F.[1], Arsyutov D.G.[2], Khodjaev N.S.[2], Boiko E.V.[3], Pravosudova M.M.[3], Chuprov A.D.[4], Kuvaitseva Yu.S.[4], Gorbunova N.Yu.[5], Markova A.A.[5], Pshenichnov M.V.[6], Postupaeva N.V.[6], Malysheva Yu.V.[7], Ivanov A.A.[7], Eremina A.V.[8], Trunov A.N.[8], Chernykh V.V.[8]

[1] Research Institute of Clinical and Experimental Lymphology – Branch of the Federal Research Center Institute of Cytology and Genetics, Siberian Branch of the Russian Academy of Sciences (IC&G SB RAS)
2 Timakov St., 630060 Novosibirsk, Russian Federation

[2] S. Fyodorov Eye Microsurgery Federal State Institution
59a Beskudnikovsky Blv., 127486 Moscow, Russian Federation

[3] Saint Petersburg branch of S. Fyodorov Eye Microsurgery Federal State Institution
21a Yaroslav Hashek St., 192283 Saint Petersburg, Russian Federation

[4] Orenburg branch of S. Fyodorov Eye Microsurgery Federal State Institution
17 Salmyshskaya St., 460047 Orenburg, Russian Federation

[5] Cheboksary branch of S. Fyodorov Eye Microsurgery Federal State Institution
10 Traktorostroiteley Ave., 428028 Cheboksary, Russian Federation

[6] Khabarovsk branch of S. Fyodorov Eye Microsurgery Federal State Institution
211 Tikhookeanskaya St., 680033 Khabarovsk, Russian Federation

[7] Irkutsk branch of S. Fyodorov Eye Microsurgery Federal State Institution
337 Lermontov St., 664033 Irkutsk, Russian Federation

[8] Novosibirsk branch of S. Fyodorov Eye Microsurgery Federal State Institution
10 Kolhidskaya St., 630096 Novosibirsk, Russian Federation

ABSTRACT

Background. Primary open-angle glaucoma (POAG) is optic neuropathy, the etiology of which is associated with genetic and non-genetic factors. *IL-10* and *MMP2* SNPs are associated with POAG, but the nature of the association depends on the ethnic profile of the population. For the Russian Federation, whose population includes 190 nationalities, this issue is relevant.

Aim. To perform a multicenter comparative analysis of the *IL-10* and *MMP2* SNPs as potential factors for predicting the development of POAG in patients in four regions of the Russian Federation: the Novosibirsk, Leningrad, and Orenburg Regions, and the Chuvash Republic.

Materials and methods. We examined 499 POAG patients from 4 branches of S. Fyodorov Eye Microsurgery Federal State Institution (main group), 530 people without visual pathology (control 1), and 100 patients with cataracts (control 2). Genotyping of *IL10* (rs1800896 and rs1800872 SNPs) and *MMP*-2 (rs243865) was performed by real-time polymerase chain reaction (RT-PCR) according to the manufacturer's instructions (Lytex and Syntol, Russia). The differences were considered statistically significant at the Bonferroni-corrected $p < 0.05$.

✉ *Konenkov Vladimir I.,* vikonenkov@gmail.com

Results. An increase in the incidence of *IL-10-1082 A* was revealed in POAG patients compared to patients with cataract and healthy individuals. An increase in the incidence of *IL-10 AA* in both regions and a decrease in the frequency of *MMP2-1306 TT* were found. Similar patterns were established for interlocus *IL-10* and *MMP2* genotypes. The group of patients in the Leningrad Region differed the most compared to other regions, which may be due to their long-term residence together with the indigenous Finno – Ugric peoples.

Conclusion. The data obtained should be taken into account when developing additional criteria for predicting predisposition to POAG, which is important in case of POAG in the family history.

Keywords: *IL-10, MMP2*, SNP, POAG

Conflict of interest. The authors declare the absence of obvious or potential conflicts of interest related to the publication of this article.

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Conformity with the principles of ethics. All study participants signed an informed consent to personal data processing. The study was approved by the Bioethics Committee at the Research Institute of Clinical and Experimental Lymphology (Minutes No. 177 dated February 2, 2003) and Novosibirsk branch of S. Fyodorov Eye Microsurgery Federal State Institution (Minutes No. 2 dated September 2, 2018).

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Межрегиональные различия распределения SNP генов *IL-10* и *MMP2* в группах пациентов с первичной открытоугольной глаукомой по данным многоцентрового исследования в Российской Федерации

Коненков В.И.[1], Шевченко А.В.[1], Прокофьев В.Ф.[1], Арсютов Д.Г.[2], Ходжаев Н.С.[2], Бойко Э.В.[3], Правосудова М.М.[3], Чупров А.Д.[4], Кувайцева Ю.С.[4], Горбунова Н.Ю.[5], Маркова А.А.[5], Пшеничнов М.В.[6], Поступаева Н.В.[6], Малышева Ю.В.[7], Иванов А.А.[7], Еремина А.В.[8], Трунов А.Н.[8], Черных В.В.[8]

[1] Научно-исследовательский институт клинической и экспериментальной лимфологии – филиал Федерального исследовательского центра «Институт цитологии и генетики Сибирского отделения Российской академии наук» (НИИКЭЛ – филиал ИЦиГ СО РАН)
Россия, 630060, г. Новосибирск, ул. Тимакова, 2

[2] Национальный медицинский исследовательский центр (НМИЦ) «Межотраслевой научно-технический комплекс (МНТК) “Микрохирургия глаза” им. акад. С.Н. Федорова»
Россия, 127486, г. Москва, Бескудниковский бульвар, 59а

[3] Санкт-Петербургский филиал НМИЦ «МНТК “Микрохирургия глаза” им. акад. С.Н. Федорова»
Россия, 192283, г. Санкт-Петербург, ул. Ярослава Гашека, 21

[4] Оренбургский филиал НМИЦ «МНТК “Микрохирургия глаза” им. акад. С.Н. Федорова
Россия, 460047, г. Оренбург, ул. Салмышская, 17

[5] Чебоксарский филиал НМИЦ «МНТК “Микрохирургия глаза” им. акад. С.Н. Федорова» Россия, 428028, Чувашская Республика, г. Чебоксары, проспект Тракторостроителей, 10

[6] *Хабаровский филиал НМИЦ «МНТК "Микрохирургия глаза" им. акад. С.Н. Федорова» Россия, 680033, г. Хабаровск, ул. Тихоокеанская, 211*

[7] *Иркутский филиал НМИЦ «МНТК "Микрохирургия глаза" им. акад. С.Н. Федорова» Россия, 664033, г. Иркутск, ул. Лермонтова, 337*

[8] *Новосибирский филиал НМИЦ «МНТК "Микрохирургия глаза" им. акад. С.Н. Федорова» Россия, 630096, г. Новосибирск, ул. Колхидская, 10*

РЕЗЮМЕ

Обоснование. Первичная открытоугольная глаукома (ПОУГ) – хроническая прогрессирующая оптиконейропатия, этиология которой связана с генетическими и негенетическими факторами. Полиморфизмы SNP генов *IL-10* и *MMP2* ассоциированы с ПОУГ, однако характер ассоциированности зависит от этнического состава населения. Для Российской Федерации, население которой состоит из представителей 190 национальностей, это актуальная проблема.

Цель исследования – многоцентровый сравнительный анализ распределения SNP генов *IL-10* и *MMP2* как потенциальных факторов прогноза развития заболевания в группах пациентов с ПОУГ в четырех регионах населения России: Новосибирской, Ленинградской и Оренбургской областей, Чувашской Республики.

Материалы и методы. Обследованы 499 пациентов с ПОУГ (основная группа) из четырех филиалов Межотраслевого научно-технического комплекса «Микрохирургия глаза», 530 человек без патологии органов зрения (контроль 1) и 100 пациентов с катарактой (контроль 2). Генотипирование генов *IL-10* (полиморфизмы rs1800896, rs1800872) и *MMP2* (полиморфизм rs243865) проводили методом полимеразной цепной реакции в реальном времени согласно инструкции фирмы производителя («Литех» и «Синтол», Россия). Статистически значимыми считались различия при $p < 0,05$ с учетом поправки Бонферрони.

Результаты. Выявлено достоверное преобладание локуса -1082 аллеля *A* (ген *IL-10)* у пациентов с ПОУГ относительно лиц с катарактой и здоровых. Установлено повышение частоты генотипа *AA* (*IL-10)* в обеих позициях и снижение частоты -1306 TT (*MMP2*). Сходные закономерности установлены для межлокусных генотипов *IL-10* и *MMP2.* Получены данные о наличии достоверных различий в характере распределения аллей, генотипов между регионами России. Наиболее отличалась от остальных регионов группа пациентов Ленинградской области, что может быть связано с ее многолетним проживанием совместно с коренным населением финно-угорского происхождения.

Заключение. Полученные данные необходимо учитывать при разработках дополнительных критериев прогноза предрасположенности к развитию ПОУГ, что актуально при наличии отягощенного семейного анамнеза.

Ключевые слова: *IL-10, MMP2*, SNP, ПОУГ

Источник финансирования. Работа выполнена в рамках договора о научно-практическом сотрудничестве между НИИКЭЛ – филиалом ИЦиГ СО РАН и Новосибирским филиалом МНТК «Микрохирургия глаза» им. акад. С.Н. Федорова Минздрава России.

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов при проведении исследования.

Соответствие принципам этики. Все участники подписали письменное информированное согласие на участие в исследовании и обработку персональных данных Исследование одобрено комитетами по биомедицинской этике НИИКЭЛ – филиалом ИЦиГ СО РАН (протокол № 177 от 02.02.2003) и Новосибирского филиала МНТК «Микрохирургия глаза» им. акад. С.Н. Федорова Минздрава России (протокол № 2 от 2.09.2018).

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INTRODUCTION

Primary open-angle glaucoma (POAG) is chronic progressive optic neuropathy that unites a group of diseases whose etiology is not fully understood. Its origin and development are predominantly explained by a multifactorial concept involving the variety of genetic and non-genetic factors [1]. Among the causes of incurable blindness in Russia, glaucoma occupies one of the leading places, exceeding the European average by 1.5–2 times [2]. In addition to genetic predisposition, disorders of aqueous humor outflow caused by impaired angiogenesis, damage to the optic nerve, and retinal ganglion cell loss play an essential role in the development of POAG [3]. Both vascular (circulatory and lymphatic vascular) networks and extravascular spaces (extracellular matrix) are involved in the aqueous humor outflow [4].

Matrix metalloproteinases (MMPs) are a family of proteolytic enzymes that break down extracellular matrix (ECM) components and are crucial in many biological processes, including the development and remodeling of tissues both in normal and pathological conditions. This family of zinc-containing endopeptidases, which catalyze degradation reactions of ECM components, consists of more than 20 enzymes in the human body. The substrates for MMP-2 are gelatinases represented by type 4 collagen, aggrecan, gelatin, and fibronectin. The activity of MMPs is affected by their expression level and the expression of tissue inhibitors of MMPs. In the eye, MMP-mediated ECM turnover in the juxtacanalicular region of the ocular trabecular meshwork reduces aqueous humor outflow resistance and helps maintain intraocular pressure homeostasis [5, 6].

MMPs are involved in the pathogenesis of various types of glaucoma; the content of MMP-2 and -9 is significantly higher in glaucomatous eyes compared to healthy ones. These changes were found in watery eye discharge, the iridocorneal angle, and the Tenon capsule in patients with POAG, primary angle-closure glaucoma, and exfoliative glaucoma. An increase in the content of MMP-9 both in the systemic circulation and locally may also indicate impaired cellular remodeling in the structures of the eye, which contributes to the formation of autoimmune inflammation with tissue destruction [7].

Associations have been established between the genotypes 1G/2G *(MMP-1* gene*)*, C/T *(MMP-9* gene*)* ($p < 0.001$), and C/T *(IL-1b* gene*)* ($p < 0.05$) and a decrease in the thickness of the retinal nerve fiber layer in the group of patients with POAG. The results showed a relationship between the reduced rim area and the A/G genotype *(MMP-12* gene*)* ($p < 0.001$). The normal value of this parameter was detected in the group of patients with POAG associated with the genotypes T/C *(TIMP1* gene) ($p < 0.05$) and C/T *(IL1b* gene) ($p < 0.05$). Finally, the results showed an association of the C/T genotype *(MMP-9* gene*)* ($p < 0.001$) with a decrease in the optic disc excavation index in the group of patients with POAG [8].

In humans, the *MMP-2* gene is located on chromosome 16. A total of 37 polymorphisms located in the *MMP-2* gene were studied, most of which are located in the promoter region. The main polymorphisms studied were rs243865, rs2285053, rs243866, and rs243864, which can affect the expression of encoded regulatory proteins.

Cytokines, and in particular the inhibitory immunosuppressive interleukin (IL)-10, play an essential role in regulating the functional activity of MMP. IL-10 stimulates tissue inhibitors of metalloproteinases (TIMPs) and inhibits the expression of MMP, thus influencing the induction of angiogenesis [9].

In humans, IL-10 is encoded by the *IL-10* gene located on the long arm of chromosome 1. The *IL-10* gene promoter is characterized by the presence of polymorphisms that can significantly affect IL-10 expression in different people [10]. Of the 49 polymorphisms identified, 46 are single-nucleotide polymorphisms (SNPs), 2 are microsatellite polymorphisms, and 1 is a small (3-letter) dropout. Twenty-eight polymorphisms occur in the promoter region of the gene, 20 polymorphisms are non-coding intronic or synonymous substitutions, and only 1 polymorphism leads to a change in the amino acid sequence of the protein.

Based on these data, we formulated the aim of the study – to conduct a multicenter comparative analysis of the distribution of three SNPs of the *IL-10* and *MMP2* genes as potential factors for predicting the development of POAG in patients in four regions of the Russian Federation: the Novosibirsk, Leningrad, and Orenburg Regions, and the Chuvash Republic. These studies are relevant for the Russian Federation, where, according to the latest population census, more than 190 nationalities of various ethnicities live.

MATERIALS AND METHODS

We performed a comparative, multicenter, case – control genetic study of 499 patients with POAG (main group) from four regions of the Russian Federation.

The patients were treated and followed up in Novosibirsk (199 people), Cheboksary (100 people), Orenburg (100 people), and Saint Petersburg (100 people) branches of S. Fyodorov Eye Microsurgery Federal State Institution. The study included patients aged 36–91 years, with a median of 71.0 [66.0; 76.0] years; 259 men (51.9%) and 240 women (48.1%).

Control group 1 (530 people) included apparently healthy individuals (157 men and 373 women) aged 18–69 years. Control group 2 encompassed 100 patients with cataract who received treatment in the Novosibirsk branch of S. Fyodorov Eye Microsurgery Federal State Institution. Relatives of the patients were not included either in the main or in the control groups.

The study was approved by the Bioethics Committees at Research Institute of Clinical and Experimental Lymphology – Branch of the Institute of Cytology and Genetics, Siberian Branch of Russian Academy of Sciences (Minutes No. 177 dated 02.02.2003) and the Novosibirsk Branch of S. Fyodorov Eye Microsurgery Federal State Institution (Minutes No. 2 dated 2.09.2018) and was carried out in accordance with the WMA Declaration of Helsinki "Ethical Principles of Conducting Medical Research Involving Humans as Subjects" (Fortaleza, Brazil, October 2013). A written informed consent was obtained from all participants to participation in the study and to personal data processing.

The inclusion criterion for the main group was stage II–III POAG with the axial length of 22.5–24.5 mm.

The exclusion criteria were the presence of any hereditary and genetic diseases, autoimmune diseases and tumors of any localization (including multiple sclerosis, diabetes mellitus of any form, cataracts (total cataract, if it made it difficult to conduct an instrumental examination), neovascular, pigmentary glaucoma, low-tension glaucoma, keratitis and uveitis of various etiology and localization, central retinal vein occlusion, central serous chorioretinopathy, wet macular degeneration, eye injuries and burns in the medical history.

The diagnosis of POAG was verified according to the developed and approved criteria set out in the clinical guidelines "Primary open-angle glaucoma" (http://avo-portal.ru/documents/fkr/Klinicheskie_rekomendacii_POUG_2022.pdf).

To assess intraocular pressure (IOP), applanation tonometry data were used. Structural pathological neuroretinal alterations were assessed following protocols for the optic disc and retinal nerve fiber layer examination (according to optical coherence tomography). Typical defects in the visual field were confirmed by the perimeter index *MD* (average deviation of photosensitivity) and narrowing of the boundaries of the visual field along the nasal isopters. Grade 3–4 opening of the iridocorneal angle was confirmed by gonioscopy. Given the fact that the Russian classification of POAG includes four clinical and pathogenetic forms (pseudoexfoliative glaucoma, chronic (simple) glaucoma, low-tension glaucoma, and pigmentary glaucoma), biomicroscopy of the anterior segment of the eye was performed. Its results allowed for the differential diagnosis and correct selection of patients. The study included patients with pseudoexfoliative glaucoma and primary simple glaucoma.

Single-nucleotide polymorphisms of the *IL10* gene (-592 C/A, rs1800872 and -1082 G/A, rs1800896) were genotyped using real-time polymerase chain reaction (RT-PCR) with the SYBR Green dye (Lytech and Syntol, Russia) on the DT-96 amplifier (DNA Technology, Russia) according to the manufacturer's instructions. DNA isolation and RT-PCR were performed using a unified instrument and reagent database at the Laboratory for Clinical Immunogenetics of the Research Institute of Clinical and Experimental Lymphology (Novosibirsk).

Statistical processing of the results was carried out using IBM SPSS Statistics 23 and specialized programs for volumetric processing of biological information, including multidimensional genetic analysis: Arlequin 3.5.2, SNPStats, and Cytoscape 3.10.3. When analyzing the results of the genetic study, the allele and genotype frequency, their poly-locus combinations, the odds ratio (OR), and the 95% confidence interval (95% CI) were calculated. The distribution of genotypes across the studied polymorphic loci was checked for compliance with the Hardy – Weinberg equilibrium using the exact Fisher's criterion. The significance level of differences in the frequency of genetic trait distribution (alleles, simple and complex genotypes) in the compared groups was determined by the two-tailed Fisher's exact test for 2 x 2 contingency tables (P_TMF2). To eliminate the effect of multiple comparisons, the Bonferroni correction was applied. The critical significance level when testing statistical hypotheses was assumed to be 0.05.

RESULTS

At the first stage of the study, it was necessary to identify groups comparing the results identified among patients with POAG with the controls. As the latter, we identified groups of healthy individuals without signs of visual organ dysfunction (control 1) as the most representative and a group of patients with cataract who did not have an increase in IOP (control 2, 100 people). The comparison group (control 1) included 530 people that matched with the main POAG group (499 people) based on gender and age. The results of comparing the distribution of the studied parameters are presented in Table 1.

Table 1

Results of the Frequency Distribution of rs243865 in the *MMP-2* Gene, rs1800896 and rs1800872 in the *IL-10* Gene in Groups of Patients with POAG and Healthy Individuals

Polymorphic region of the gene	Alleles/ genotypes	POAG	Donors				
		Frequency, %		OR	OR_CI95	*p*_TMF2	*p*_COR
IL10-592	C	77.5	79.9	0.86	0.69–1.07	0.187	0.374
IL10-592	A	22.6	20.1	1.16	0.93–1.44	0.187	0.374
IL10-1082	A	63.1	49.8	1.73	1.38–2.16	0.000	0.000
IL10-1082	G	36.9	50.2	0.58	0.46–0.73	0.000	0.000
MMP2-1306	C	75.7	74.6	1.06	0.84–1.33	0.639	1.278
MMP2-1306	T	24.4	25.4	0.95	0.75–1.19	0.639	1.278
IL10-592	CC	60.7	62.6	0.93	0.72–1.20	0.556	1.669
IL10-592	CA	33.5	34.8	0.94	0.72–1.23	0.687	2.061
IL10-592	AA	5.8	2.7	2.25	1.15–4.37	0.017	0.052
IL10-1082	AA	38.5	22.8	2.12	1.48–3.04	0.000	0.000
IL10-1082	AG	49.3	54.0	0.83	0.60–1.14	0.260	0.781
IL10-1082	GG	12.2	23.2	0.46	0.31–0.69	0.000	0.001
MMP2-1306	CC	55.7	57.1	0.95	0.71–1.26	0.718	2.155
MMP2-1306	CT	39.9	35.1	1.23	0.92–1.64	0.184	0.552
MMP2-1306	TT	4.4	7.8	0.54	0.39–0.98	0.045	0.136
IL10-592:IL10-1082	CC-AA	17.0	10.8	1.69	1.04–2.75	0.033	0.260
IL10-592:IL10-1082	CC-AG	32.7	32.9	0.99	0.71–1.39	1.000	8.000
IL10-592:IL10-1082	CC-GG	11.0	18.9	0.53	0.34–0.82	0.006	0.050
IL10-592:IL10-1082	CA-AA	16.6	9.9	1.81	1.10–2.99	0.022	0.174
IL10-592:IL10-1082	CA-AG	15.6	20.7	0.71	0.47–1.06	0.109	0.869
IL10-592:IL10-1082	CA-GG	1.2	4.5	0.26	0.09–0.72	0.011	0.085
IL10-592:IL10-1082	AA-AA	4.8	1.8	2.75	0.94–8.03	0.060	0.483
IL10-592:IL10-1082	AA-AG	1.0	0.5	2.24	0.26–19.26	0.672	5.378
IL10-592:MMP2-1306	CC-CC	35.1	32.9	1.10	0.82–1.49	0.544	4.352
IL10-592:MMP2-1306	CC-CT	22.7	24.6	0.90	0.64–1.25	0.551	4.411
IL10-592:MMP2-1306	CC-TT	3.0	5.1	0.58	0.28–1.18	0.136	1.09
IL10-592:MMP2-1306	CA-CC	17.2	21.4	0.76	0.54–1.09	0.141	1.131
IL10-592:MMP2-1306	CA-CT	14.8	10.5	1.48	0.95–2.29	0.088	0.706
IL10-592:MMP2-1306	CA-TT	1.4	2.9	0.48	0.18–1.30	0.193	1.547
IL10-592:MMP2-1306	AA-CC	3.4	2.2	1.54	0.63–3.76	0.399	3.194
IL10-592:MMP2-1306	AA-CT	2.4	0.3	7.69	0.99–54.42	0.021	0.169
IL10-1082:MMP2-1306	AA-CC	20.2	11.9	1.88	1.17–3.01	0.007	0.065
IL10-1082:MMP2-1306	AA-CT	17.2	9.5	1.98	1.18–3.31	0.008	0.072
IL10-1082:MMP2-1306	AA-TT	1.0	1.4	0.70	0.17–2.95	0.700	6.300
IL10-1082:MMP2-1306	AG-CC	28.7	27.6	1.05	0.73–1.51	0.855	7.697
IL10-1082:MMP2-1306	AG-CT	18.0	21.9	0.78	0.53–1.17	0.251	2.257
IL10-1082:MMP2-1306	AG-TT	2.6	3.8	0.68	0.28–1.65	0.467	4.196

End of Table 1

Polymorphic region of the gene	Alleles/ genotypes	POAG	Donors				
		Frequency, %		OR	OR_CI95	*p*_TMF2	*p*_COR
IL10-1082:MMP2-1306	GG-CC	6.8	15.2	0.41	0.24–0.68	0.001	0.009
IL10-1082:MMP2-1306	GG-CT	4.6	7.1	0.63	0.32–1.23	0.201	1.805
IL10-1082:MMP2-1306	GG-TT	0.8	1.4	0.56	0.12–2.51	0.428	3.856
IL10-592:IL10-1082:MMP2-1306	CC-AA-CC	9.6	3.8	2.67	1.24–5.76	0.009	0.187
IL10-592:IL10-1082:MMP2-1306	CC-GG-CC	6.2	11.5	0.51	0.29–0.89	0.021	0.437
IL10-592:IL10-1082:MMP2-1306	CA-AA-CT	7.8	2.4	3.46	1.34–8.90	0.006	0.120
IL10-592:IL10-1082:MMP2-1306	CA-GG-CC	0.6	3.8	0.15	0.04–0.58	0.004	0.076
IL10-592:IL10-1082:MMP2-1306	AA-AA-CT	2.2	0.0	5.15	0.67–39.89	0.040	0.832

Note. Here and in Table 2: *p*_TMF2 – significance of the two-ailed Fisher's exact test; *p*_COR – Bonferroni-corrected significance.

As seen from the data presented, the distribution of *IL-10* gene alleles at position *-592* and *MMP2* gene alleles at position *-1306* was similar in both compared groups, whereas at position *-1082*, significant predominance of allele *A* among patients was revealed.

For the SNP genotypes of the *IL-10* gene, an increase in the frequency of homozygous *AA* variants at both positions and a decrease in the frequency of the homozygous *TT* variant of the *MMP2* gene in the position *-1306* were found. A slight increase in the frequency of *CC-AA* and *CA-AA* genotypes was also detected in the group of patients with POAG, along with a decrease in the frequency of *IL-10* genotypes containing the *G* allele.

Similar patterns were established for the interlocus genotypes of the *IL-10* and *MMP2* genes, which are characterized by a combination of alleles A and C at positions -592 and -1082 and double homozygotes GG / CC at position -1082. Minor multidirectional changes were revealed for three-locus combinations.

The conducted studies of patients from the Novosibirsk branch S. Fyodorov Eye Microsurgery Federal State Institution showed that, unlike the control group of patients with cataracts who did not have an increase in IOP, a significant decrease in the frequency of the homozygous *TT* variant of the *MMP-2* gene at position *-1306* (OR = 0.33; *p*_ cor = 0.0258) was also found among patients with POAG. Moreover, this pattern persisted in the complex genotype *IL10-1082:MMP2-1306 AA-TT* (OR = 0.07; *p*_cor = 0.0207) and with lower reliability in the complex genotype *IL10-592:IL10-1082:MMP2-1306 CC-AA-TT* (OR = 0.08; *p*_ TMF2 = 0.0039; *p*_cor = 0.08). This conclusion was also verified by comparing the data obtained in a group of patients with POAG with the results of the study of healthy individuals (526 people) used as an additional control group. The frequency of distribution of the homozygous *TT* variant at *MMP2-1306* position among patients with POAG was also significantly lower (OR = 0.54; *p* = 0.045) than among healthy individuals without identified eye diseases.

Based on the above data, these results can be interpreted as indirect evidence that the level of MMP-2 expression in patients with POAG should be higher, which can be regarded as one of the possible factors of ECM disorders in this eye disease. For our multinational country, it is interesting to see how common the data obtained are for a number of regions of the Russian Federation, or whether there are significant differences in these distributions. To get an answer to this question, we conducted a joint study with branches of S. Fyodorov Eye Microsurgery Federal State Institution located in such regions as Saint Petersburg, Orenburg, Cheboksary, and Novosibirsk. The results of this multicenter study are presented in Table 2.

The results presented in Table 2 show that interregional differences were revealed in a number of analyzed genetic parameters between the patient groups from the Novosibirsk Region and the Chuvash Republic, which is probably due to different representation of the Mongoloid population in these regions, with predominantly white population. It was found that the frequency of the *TT* genotype in the position *-1306* of the *IL-10* gene was increased among patients from the NSR, while it was completely absent in patients from the CHR.

Differences between the Distribution Parameters of rs243865 of the *MMP-2* Gene and rs1800896 and rs1800872 of the *IL-10* Gene in Groups of Patients with POAG according to the Data of Four Branches of S. Fyodorov Eye Microsurgery Federal State Institution (Frequency is Indicated in %)

Polymorphic genotypes		NSR	CHR	OR	LR	*p*_ TMF2	*p*_ TMF2	*p*_ TMF2	*p*_ TMF2	*p*_ TMF2	*p*_ TMF2	*p*_cor	*p* _cor	*p*_cor	*p*_cor	*p*_cor	*p*_cor
		1	2	3	4	1-2	1-3	1-4	2-3	2-4	3-4	1-2	1-3	1-4	2-3	2-4	3-4
MMP2-1306	*C*	74.9	74.5	78.0	76.0	0.920	0.419	0.841	0.481	0.817	0.722	1.842	0.838	1.682	0.962	1.634	1.443
MMP2-1306	*T*	25.1	25.5	22.0	24.0	0.920	0.419	0.841	0.481	0.817	0.727	1.842	0.830	1.682	0.962	1.634	1.443
MMP2-1306	*CC*	55.3	49.0	58.0	61.0	0.327	0.711	0.387	0.257	0.118	0.773	0.982	2.134	1.160	0.770	0.353	2.320
MMP2-1306	*CT*	39.2	51.0	40.0	30.0	0.063	0.901	0.127	0.155	0.004	0.182	0.190	2.702	0.382	0.466	0.011	0.546
MMP2-1306	*TT*	5.5	0.0	2.0	9.0	0.018	0.232	0.326	0.497	0.003	0.058	0.055	0.695	0.980	1.493	0.010	0.176
IL10-592:MMP2-1306	*CC-CC*	30.2	31.0	39.0	45.0	0.895	0.152	0.015	0.299	0.058	0.474	7.157	1.2144	0.116	2.096	0.463	3.791
IL10-592:MMP2-1306	*CC-CT*	17.1	34.0	18.0	27.0	0.001	0.872	0.049	0.015	0.357	0.175	0.010	6.978	0.394	0.106	2.855	1.401
IL10-592:MMP2-1306	*CC-TT*	4.0	0.0	0.0	7.0	0.055	0.053	0.273		0.014	0.014	0.442	0.442	2.185		0.112	0.112
IL10-592:MMP2-1306	*CA-CC*	21.6	14.0	16.0	13.0	0.122	0.283	0.084	0.843	1.000	0.689	0.974	2.266	0.674	5.903	8.000	5.508
IL10-592:MMP2-1306	*CA-CT*	20.1	14.0	19.0	1.0	0.207	0.879	0.000	0.446	0.001	0.000	1.659	7.028	0.001	3.125	0.005	0.001
IL10-592:MMP2-1306	*CA-TT*	1.5	0.0	2.0	2.0	0.553	1.000	1.000	0.497	0.498	1.000	4.426	8.000	8.000	3.483	3.980	8.000
IL10-592:MMP2-1306	*AA-CC*	3.5	4.0	3.0	3.0	1.000	1.000	1.000	1.000	1.000	1.000	8.000	8.000	8.000	7.000	8.000	8.000
IL10-592:MMP2-1306	*AA-CT*	2.0	3.0	3.0	2.0	0.690	0.690	1.000	1.000	1.000	1.000	5.521	5.521	8.000	7.000	8.000	8.000
IL10-1082:MMP2-1306	*AA-CC*	20.6	18.0	19.0	23.0	0.646	0.879	0.656	1.000	0.484	0.603	5.817	7.907	5.900	7.000	4.355	5.426
IL10-1082:MMP2-1306	*AA-CT*	12.6	26.0	21.0	14.0	0.003	0.063	0.719	0.505	0.051	0.264	0.048	0.567	6.474	3.535	0.458	2.376
IL10-1082:MMP2-1306	*AA-TT*	0.5	0.0	2.0	2.0	1.000	0.260	0.260	0.497	0.498	1.000	9.000	2.340	2.340	3.483	4.478	9.000
IL10-1082:MMP2-1306	*AG-CC*	27.1	21.0	36.0	32.0	0.262	0.141	0.417	0.028	0.109	0.655	2.357	1.273	3.757	0.195	0.977	5.891
IL10-1082:MMP2-1306	*AG-CT*	21.6	19.0	16.0	12.0	0.652	0.283	0.057	0.710	0.241	0.542	5.870	2.550	0.511	4.971	2.167	4.874
IL10-1082:MMP2-1306	*AG-TT*	3.5	0.0	0.0	6.0	0.100	0.100	0.371		0.029	0.029	0.898	0.898	3.340		0.260	0.260
IL10-1082:MMP2-1306	*GG-CC*	7.5	10.0	3.0	6.0	0.509	0.196	0.811	0.082	0.435	0.498	4.582	1.760	7.301	0.573	3.918	4.479
IL10-1082:MMP2-1306	*GG-CT*	5.0	6.0	3.0	4.0	0.787	0.554	0.780	0.498	0.748	1.000	7.085	4.990	7.021	3.484	6.728	9.000
IL10-1082:MMP2-1306	*GG-TT*	1.5	0.0	0.0	1.0	0.553	0.553	1.000		1.000	1.000	4.9	4.980	9.000		9.000	9.000
IL10-592:IL10-1082:MMP2-1306	*CC-AA-CC*	8.0	7.0	8.0	17.0	0.822	1.000	0.030	1.000	0.048	0.086	16.442	19.000	0.600	16.000	0.968	1.626
IL10-592:IL10-1082:MMP2-1306	*CC-AA-CT*	1.5	17.0	5.0	11.0	0.000	0.123	0.001	0.012	0.308	0.191	0.002	2.335	0.010	0.184	6.166	3.638
IL10-592:IL10-1082:MMP2-1306	*CC-AA-TT*	0.0	0.0	0.0	1.0			0.334		1.000	1.000			6.688		20.00	19.00
IL10-592:IL10-1082:MMP2-1306	*CC-AG-CC*	15.1	14.0	29.0	23.0	0.864	0.006	0.108	0.015	0.145	0.420	17.282	0.105	2.168	0.245	2.890	7.988
IL10-592:IL10-1082:MMP2-1306	*CC-AG-CT*	10.6	14.0	10.0	12.0	0.446	1.000	0.700	0.514	0.834	0.822	8.922	19.000	1.994	8.234	16.678	15.612

Endof Table 2

Polymorphic genotypes		NSR	CHR	OR	LR	*p*_ TMF2	*p*_ TMF2	*p*_ TMF2	*p*_ TMF2	*p*_ TMF2	*p*_ TMF2	*p*_cor	*p* _cor	*p*_cor	*p*_cor	*p*_cor	*p*_cor
		1	2	3	4	1-2	1-3	1-4	2-3	2-4	3-4	1-2	1-3	1-4	2-3	2-4	3-4
IL10-592:IL10-1082:MMP2-1306	*CC-AG-TT*	2.5	0.0	0.0	5.0	0.173	0.173	0.311		0.059	0.059	3.456	3.283	6.216		1.188	1.129
IL10-592:IL10-1082:MMP2-1306	*CC-GG-CC*	7.0	10.0	2.0	5.0	0.375	0.100	0.619	0.033	0.283	0.445	7.504	1.896	12.386	0.528	5.656	8.451
IL10-592:IL10-1082:MMP2-1306	*CC-GG-CT*	5.0	3.0	3.0	4.0	0.554	0.554	0.780	1.000	1.000	1.000	11.088	10.534	15.602	16.000	20.000	19.000
IL10-592:IL10-1082:MMP2-1306	*CC-GG-TT*	1.5	0.0	0.0	1.0	0.553	0.553	1.000		1.000	1.000	11.066	10.513	20.000		20.000	19.000
IL10-592:IL10-1082:MMP2-1306	*CA-AA-CC*	10.1	8.0	9.0	3.0	0.676	0.839	0.037	1.000	0.213	0.134	13.524	15.935	0.742	16.000	4.268	2.542
IL10-592:IL10-1082:MMP2-1306	*CA-AA-CT*	9.6	6.0	13.0	1.0	0.378	0.428	0.005	0.146	0.118	0.001	7.566	8.134	0.108	2.342	2.368	0.025
IL10-592:IL10-1082:MMP2-1306	*CA-AA-TT*	0.5	0.0	2.0	1.0	1.000	0.260	1.000	0.498	1.000	1.000	20.000	4.940	20.000	7.960	20.000	19.000
IL10-592:IL10-1082:MMP2-1306	*CA-AG-CC*	11.1	6.0	6.0	9.0	0.207	0.207	0.689	1.000	0.593	0.593	4.144	3.937	13.790	16.000	11.856	11.263
IL10-592:IL10-1082:MMP2-1306	*CA-AG-CT*	10.6	5.0	6.0	0.0	0.130	0.284	0.000	1.000	0.059	0.029	2.600	5.404	0.004	16.000	1.1880	0.549
IL10-592:IL10-1082:MMP2-1306	*CA-AG-TT*	1.0	0.0	0.0	1.0	0.553	0.553	1.000		1.000	1.000	11.066	10.5130	20.000		20.000	19.000
IL10-592:IL10-1082:MMP2-1306	*CA-GG-CC*	0.5	0.0	1.00	1.0	1.000	1.000	1.000	1.000	1.000	1.000	20.000	19.000	20.000	16.000	20.000	19.000
IL10-592:IL10-1082:MMP2-1306	*CA-GG-CT*	0.0	3.0	0.00	0.0	0.037			0.246	0.246		0.734			3.939	4.924	
IL10-592:IL10-1082:MMP2-1306	*AA-AA-CC*	2.5	3.0	2.0	3.0	1.000	1.000	1.000	1.000	1.000	1.000	20.000	19.000	20.000	16.000	20.000	19.000
IL10-592:IL10-1082:MMP2-1306	*AA-AA-CT*	1.5	3.0	3.0	2.0	0.405	0.405	1.000	1.000	1.000	1.000	8.108	7.703	20.000	16.000	20.000	19.000
IL10-592:IL10-1082:MMP2-1306	*AA-AG-CC*	1.0	1.0	1.0	0.0	1.000	1.000	0.553	1.000	1.000	1.000	20.000	19.000	11.066	16.000	20.000	19.000
IL10-592:IL10-1082:MMP2-1306	*AA-AG-CT*	0.5	0.0	0.0	0.0	1.000	1.000	1.000				20.000	19.000	20.000			

Note. 1-NSR – Novosibirsk Region, 2-CHR – Chuvash Republic, 3-OR – Orenburg Region,4-LR – Leningrad Region.

At the same time, an increase in the frequency of two-locus genotypes (CC-CT IL10-592:MMP2-1306; AA-CTIL10-1082:MMP2-1306) and three-locus genotypes (IL10-592:IL10-1082:MMP2-1306 CC-AA-CT, and CA-GG-CT IL10-592:IL10-1082:MMP2-1306) was noted in this region. The latter was identified exclusively in patients from the CHR and never occurred in patients of the other three regions. Perhaps this is due to the greater proportion of the Mongoloid population in this region of the Russian Federation.

The group of patients from the Orenburg Region appeared to be more similar in the distribution of the studied parameters to the population of the NSR. In this group, only one difference was found related to an increase in the frequency of the CC-AG-CC IL10-92:IL10-1082:MMP2-1306 genotype.

The group of patients from the Leningrad Region differed the most compared to other regions, which may be due to their long-term residence together with the indigenous Finno – Ugric peoples. Among patients in this region, an increase in the frequency of CC-CC IL10-592:MMP2-1306; CC-CTIL10-592:MMP2-1306; CC-AA-CC IL10-592:IL10-1082:MMP2-1306; CC-AA-CT IL10-592:IL10-1082:MMP2-1306 genotypes was revealed. Along with this, there was a decrease in the distribution frequency of genotypes CA-CT IL10-592:MMP2-1306; CA-AA-CC IL10-592:IL10-1082:MMP2-1306; CA-AA-CTIL10-592:IL10-1082:MMP2-1306, and CA-AG-CT IL10-592: IL10-1082:MMP2-1306. At the same time, the frequency of the last two traits ranged from 0.00 to 1.00.

DISCUSSION

The interim conclusion in this section of the study may be significant differences in the detection rates of the studied polygenic parameters for the association of POAG with SNPs of functionally related genes, with the establishment of significant differences between significant groups of patients in the studied regions of the Russian Federation. This speaks of a necessity to use regional standards in the development of prognostic criteria for individual's predisposition to the development of POAG, even in case of POAG in the family history. For such a multinational country as the Russian Federation, this is a prerequisite for the development of personalized approaches in medicine.

Since vascular and capillary networks are integrated into the ECM space, regulation of its metabolism and regulation of angiogenesis are also interdependent. The processes of angiogenesis are under the control of numerous families of cytokines, chemokines, and growth factors with complex effects on the vascular and extravascular pathways of aqueous humor, blood, and lymph and their interactions with each other [11, 12]. In addition to a large family of proangiogenic factors, cytokines with an antiangiogenic effect, of which IL-10 is one of the most important, also play a significant role in maintaining the homeostasis of aqueous humor outflow.

The single nucleotide polymorphism *IL-10 -1082* and the haplotype *-1082, -819, -592* are associated with different expression of IL-10 *in vitro*, while haplotype *-1082 A/ -819 T/ -592 A* is associated with reduced expression of IL-10 compared to haplotype *-1082 G/ -819 C/ -592 C*. It is believed that up to 75% of individual differences in IL-10 expression may be due to genetic differences [13].

There is evidence that IL-10 exerts its immunosuppressive effect, including by inhibiting angiogenesis. For example, IL-10 has been shown to stimulate TIMPs and inhibit the expression of MMPs, thus affecting the induction of angiogenesis [9].

In addition, during neuroinflammation, characteristic of POAG, M2 macrophages, producing IL-10, are able to inhibit the synthesis of MMP-9, which leads to a decrease in macrophage infiltration of tissues, blockade of T cell activation and differentiation, and destruction of myelin [14]. Activation of nuclear factor kappa B (NFκB) during neuroinflammation also leads to a decrease in IL-10 synthesis [15].

The *MMP-2* rs243865 polymorphism is represented by the substitution C→T at position -1306 in the promoter. This variant disrupts binding to stimulating protein 1 (Sp1), which is a gene transcription factor, which leads to a decrease in MMP-2 expression [16]. In the meantime, the presence of the C allele in this position in the human genome leads to an increase in the concentration of MMP-2 in the circulation [17].

Thus, the substitutions of all three SNPs studied by us in promoter regions are associated with the expression of regulatory proteins encoded by these genes, and their presence in the human genome has an impact on the state of ECM, which may trigger a genetic predisposition to diseases associated with these processes.

It is important to note that the detected patterns of the association of POAG with SNPs of *IL-10* and *MMP2* genes in the Russian population are not exhaustive in terms of the involvement of polymorphic regions of cytokine genes.

Thus, associations of the predisposition to the development of POAG among the population of

Southern Russia with SNPs of the *TNFα* and *IL1b* genes were established, and respondents with the rare 308A allele and carriers of the 308G/A +308A/A genotypes showed an increase in the TNFα level in tear fluid – 49 (14.0–90.0) pg / ml compared to patients with the 308G/G genotype [18].

Our studies of the population of Western Siberia have shown a decrease in the frequency of the minor IL 1B-31*CC genotype, the IL8-251*TT genotype, and the complex IL8-251*TT:IL17-197*AA genotype. Differences in the distribution of genotypes positively and negatively correlated with the pathology were identified [19].

In the work by A. Golshan-Tafti et al. (2024), which included 442 cases and 672 controls, the IL-10 -592C>A, -819T>C, and -1082A>G polymorphisms were studied. A significant association was found between -592C>A, -819T>C, and -1082A>G in the *IL-10* gene and predisposition to POAG among the Mongoloid population [20].

It was shown that polymorphic loci *MMP-1* rs1799750 and *MMP-9* rs2250889, which play the most significant role in the formation of susceptibility to POAG (they are part of the largest number of SNP × SNP interaction models associated with the development of the disease), exert an important function in the body. The *MMP1*rs1799750 polymorphism is located in the regulatory region of DNA motifs interacting with regulatory proteins CFOS and GATA2 and is associated with the expression level of three genes (*MMP1, MMP10*, and *WTAPP1*).

The polymorphic locus rs2250889 determines a non-synonymous substitution in the *MMP-9* gene (p.Arg574Pro), is localized in an evolutionarily conserved DNA region, and is associated with the transcription level of three genes (*PLTP, PCIF1*, and *NEURL2*) and the level of alternative splicing of the *SLC12A5* gene transcript [7].

According to the 2019 meta-analysis data for the rs1799750 SNP in the *MMP* gene, a comprehensive analysis of four studies (885 POAG cases and 875 control cases) showed that rs1799750 significantly correlated with POAG in the recessive model [21].

CONCLUSION

The data obtained should be taken into account not only when analyzing the possible involvement of cytokine and metalloproteinase gene polymorphisms in the genetic predisposition to the development of POAG, but also when trying to elaborate additional criteria for predicting individual predisposition to the development of POAG, which is especially relevant with a family history of the disease. In some cases, markers of a relative risk of developing the pathology in the group analysis reach very substantial values, although not reliable.

Undoubtedly, the transition from the analysis of the association of single SNPs of a single gene to a comprehensive analysis using interlocus combinations of SNPs of a number of functionally related genes is promising. While reducing the prevalence of such polygenic traits in patient groups, it will significantly increase the information and prognostic value of identifying such genetic complexes as additional personalized prognostic features. For conducting such clinical and genetic studies, regional standards for comparing data obtained in patient groups and in randomized comparison groups can be recommended.

REFERENCES

1. Primary Open-Angle Glaucoma. Clinical Guidelines. M.: Ministry of Healthcare of Russia, 2020:58. (In Russ.).
2. Libman E.S., Shakhova E.V. Blindness and Disability due to Pathology of Vision in Russia. *Vestnik Oftal'mologii*. 2006;1:35–37. (In Russ.).
3. Youngblood H., Hauser M.A., Liu Y. Update on the Genetics of Primary Open-Angle Glaucoma. *Exp. Eye Res*. 2019;188 107795. DOI: 10.1016/j.exer.107795.
4. Ramos T., Parekh M., Meleady P., O'Sullivan F., Stewart R.M.K., Kaye S.B. et al. Specific Decellularized Extracellular Matrix Promotes the Plasticity of Human Ocular Surface Epithelial Cells. *Front. Med. (Lausanne*). 2022;9:974212:1–20. DOI: 10.3389/fmed.2022.974212.
5. Weinreb R.N., Robinson M.R., Dibas M., Stamer W.D. Matrix Metalloproteinases and Glaucoma Treatment. *J. Ocul. Pharmacol. Ther.* 2020;36(4):208–228. DOI: 10.1089/jop.2019.0146.
6. Shadrina A.S., Plieva Y.Z., Kushlinskiy D.N. Morozov A.A., Filipenko M.L., Chang V.L. et al. Classification, Regulation of Activity, and Genetic Polymorphism of Matrix Metalloproteinases in Health and Disease. *Almanac of Clinical Medicine*. 2017;45(4):266–279. (In Russ.). DOI: 10.18786/2072-0505-2017-45-4-266-279.
7. Svinareva D.I. The Contribution of Gene – Gene Interactions of Polymorphic Loci of Matrix Metalloproteinases to Susceptibility to Primary Open-Angle Glaucoma in Men. *Research Results in Biomedicine*. 2020;6(1):63–77. (In Russ.). DOI: 10.18413/2658-6533-2020-6-1-0-6.
8. Markiewicz L., Majsterek I., Przybylowska K., Dziki L., Waszczyk M., Gacek M. et al. Gene Polymorphisms of the MMP1, MMP9, MMP12, IL1b and TIMP1 and the Risk of Primary Open-Angle Glaucoma. *Acta Ophthalmol*. 2013;91:e516–e523. DOI: 10.1111/aos.
9. Stearns M.E., Wang M., Hu Y., Garcia F.U., Rhim A.B. Interleukin 10 Blocks Matrix Metalloproteinase-2 and Membrane Type 1-Matrix Metalloproteinase Synthesis in Primary Human

Prostate Tumor Lines. *J. Clin Cancer Res*. 2003;9(3):1191–1199.
10. Ouyang W., O'Garra A. Il-10 Family Cytokines Il-10 and Il-22: From Basic Science to Clinical Translation. *Immunity.*2019;50(4):871–891. DOI: 10.1016/j.immuni.2019.03.020.
11. Rakhmanov V.V., Sokolov D.I., Selkov S.A., Astakhov Yu.S., Astakhov S.Yu. Role of Cytokines in the Pathogenesis of Glaucoma. *Vestnik RAMN*. 2020;75(6):609–616. (In Russ.). DOI: 10.15690/vramn1289.
12. Geindreau M., Bruchard M., Vegran F. Role of Cytokines and Chemokines in Angiogenesis in a Tumor Context. *Cancers.* 2022;14(10):2446. DOI: 10.3390/cancers14102446.
13. Howell M.W. Interleukin-10 Gene Polymorphisms and Cancer. Madame Curie Bioscience Database [Internet]. National Center for Biotechnology Information; 2010-2013. Bookshelf Copyright Notice, 2011. URL: https://www.ncbi.nlm.nih.gov/books/about/copyright/
14. Nurdianto A.R., Arwati H., Dachlan Y.P., Febiyanti D.A. The Relationship of Hemoglobin, Interleukin-10 and Tumor Necrosis Factor Alpha Levels in Asymptomatic Malaria Patients in Trenggalek. Jawa Timur, Indonesia. *Mol. Cell Biomed Sci*. 2019;3(1):13–16. DOI: 10.21705/mcbs.v3i1.37.
15. Sidharta B.R.A., Purwanto B., Wasita B., Widyaningsih V., Soetrisno S. Single or Divided Administration of Cisplatin Can Induce Inflammation and Oxidative Stress in Male Sprague-Dawley Rats. *Indones. Biomed J*. 2022;14(2):164–171. DOI: 10.18585/inabj.v14i2.1745.
16. Dofara S.G., Chang S.L. Dioreo C. Gene Polymorphisms and Circulating Levels of MMP-2 and MMP-9: a Review of Their Role in Breast Cancer Risk. *Anticancer Research*. 2020;40(7):3619–3631. DOI: 10.21873/anticanres.14351.
17. Belo V.A., Luizon M.R., Carneiro P.C., Gomes V.A., Lacchini R., Lanna C.M. Effect of Metabolic Syndrome Risk Factors and MMP-2 Genetic Variations on Circulating MMP-2 Levels in Childhood Obesity. *Mol. Biol. Rep*. 2013;40(3):2697–704. DOI: 10.1007/s11033-012-2356-7.
18. Barycheva L.Yu., Kakulia D.M., Minasyan M.M., Kuznetsova V.V., Kozmova N.A. Polymorphism of Proinflammatory Interleukin Genes in Primary Open-Angle Glaucoma. *Medical Immunology*. 2024;26(2):303–312. (In Russ.). DOI: 10.15789/1563-0625-POP-2878.
19. Shevchenko A.V., Prokof'ev V.F., Konenkov V.I., Chernykh V.V., Ermakova O.V., Trunov A.N. Analysis of IL1B (rs1143627), IL4 (rs2243250), IL6 (rs1800795), IL8 (rs4073), IL10 (rs1800896, rs1800872), IL17A (rs227593) Cytokine Gene Polymorphism and Its Complex Genotypes among Caucasian Patients of Western Siberia with Primary Open-Angle Glaucoma. *Immunology*. 2021;42(3):211–221. (In Russ.). DOI: 10.33029/0206-4952-2021-42-3-211-221.
20. Golshan-Tafti A., Bahrami M., Mohsenzadeh-Yazdi R., Dastgheib S.A., Aghasipour M., Shiri A. et al. Consolidating Data on the Association of IL-6 And IL-10 Polymorphisms with the Development of Glaucoma: A Meta-Analysis. *Ophthalmic Genetics.* 2024;45(4):321–331. DOI: 10.1080/13816810.2024.2336964.
21. Chen M., Yu H., Xu J., Ma J., Chen X., Chen B. et al. Association of Gene Polymorphisms with Primary Open Angle Glaucoma: A Systematic Review and Meta-Analysis. *Invest. Ophthalmol. Vis. Sci*. 2019;(60):1105–1121. DOI: 10.1167/iovs.18-25922.

Author Contribution

Konenkov V.I. – carrying out a multicenter clinical and ophthalmological examination, writing Introduction and Conclusion sections of the article. Shevchenko A.V. – conducting genotyping, editing the Results section of the article. Prokofiev V.F. – conducting bioinformatic analysis of the results, editing sections of the article, performing statistical analysis. Arsyutov D.G. – carrying out a multicenter clinical and ophthalmological examination, editing the article. Khodjaev N.S., Boiko E.V., Chuprov A.D., Gorbunova N.Yu., Pshenichnov M.V., Chernykh V.V. – carrying out a clinical and ophthalmological examination, verifying the diagnosis of primary open-angle glaucoma, approving groups of patients included in the study, taking into account the criteria for inclusion and exclusion from the study. Pravosudova M.M., Kuvaitseva Yu.S., Markova A.A., Postupaeva N.V., Malysheva Yu.V., Ivanov A.A., Eremina A.V. – conducting a clinical and ophthalmological examination, compiling groups of patients included in the study. Trunov A.N. – carrying out a clinical and ophthalmological examination, verifying the diagnosis of primary open-angle glaucoma, editing the article.

Author Information

Konenkov Vladimir I. – Dr. Sci. (Med.), Professor, Academician of RAS, Research Supervisor at the Research Institute of Clinical and Experimental Lymphology, Branch of IC&G SB RAS, Novosibirsk, vikonenkov@gmail.com, https://orcid.org/0000-0001-7385-6270

Shevchenko Alla V. – Dr. Sci. (Biol.), Research Institute of Clinical and Experimental Lymphology, Branch of IC&G SB RAS, Novosibirsk, shalla64@mail.ru, https://orcid.org/0000-0001-5898-950X

Prokofiev Viktor F. – Cand. Sci. (Med.), Research Institute of Clinical and Experimental Lymphology, Branch of IC&G SB RAS, Novosibirsk, vf_prok@mail.ru, https://orcid.org/0000-0001-7290-1631

Arsyutov Dmitry G. – Cand. Sci. (Med.), S. Fyodorov Eye Microsurgery Federal State Institution, Moscow, fcc@mntk.ru, https://orcid.org/000-0002-2618-5256

Khodjaev Nazrulla S. – Dr. Sci. (Med.), Professor, S. Fyodorov Eye Microsurgery Federal State Institution, Moscow, nskhodjaev@mail.ru, https://orcid.org/0000-0002-7614-628X

Boiko Ernest V. – Dr. Sci. (Med.), Professor, Honored Doctor of the Russian Federation, Director of Saint Petersburg branch of S.Fyodorov Eye Microsurgery Federal State Institution, Saint Petersburg, boiko111@list.ru, https://orcid.org/0000-0002-7413-7478

Pravosudova Marina M. – Cand. Sci. (Med.), Head of the Clinical Expert Department of Saint Petersburg branch of S. Fyodorov Eye Microsurgery Federal State Institution, Saint Petersburg, mpravosudova52@gmail.com, https://orcid.org/0009-0003-8322-579X

Chuprov Aleksandr D. – Dr. Sci. (Med.), Professor, Director of Orenburg branch of S. Fyodorov Eye Microsurgery Federal State Institution, Orenburg, nauka@ofmntk.ru, https://orcid.org/0000-0001-7011-4220

Kuvaitseva Yuliya S. – Ophthalmologist, Orenburg branch of S. Fyodorov Eye Microsurgery Federal State Institution, Orenburg, nauka@ofmntk.ru, https://orcid.org/0000-0001-9544-1308

Gorbunova Nadezhda Yu. – Cand. Sci. (Med.), Head of the Glaucoma Surgery Department, Cheboksary branch of S. Fyodorov Eye Microsurgery Federal State Institution, Cheboksary, ngorbunova_21@mail.ru, https://orcid.org/0000-0002-7388-5634

Markova Anna A. – Cand. Sci. (Med.), Ophthalmologist, Glaucoma Surgery Department, Cheboksary branch of S. Fyodorov Eye Microsurgery Federal State Institution, Cheboksary, dr.anya@list.ru, https://orcid.org/0000-0002-4252-6487

Pshenichnov Maxim V. – Cand. Sci. (Med.), Khabarovsk branch of S. Fyodorov Eye Microsurgery Federal State Institution, Khabarovsk, naukakhvmntk@mail.ru, https://orcid.org/0000-0002-4879-1900

Postupaeva Natalia V. – Cand. Sci. (Med.), Ophthalmologist, Khabarovsk branch of S. Fyodorov Eye Microsurgery Federal State Institution, Khabarovsk, naukakhvmntk@mail.ru, https://orcid.org/0000-0002-5364-4964

Malysheva Yulia V. – Irkutsk branch of S. Fyodorov Eye Microsurgery Federal State Institution, Irkutsk, mal-julia@bk.ru, https://orcid.org/0000-0002-4200-5649

Ivanov Andrey A. – Irkutsk branch of S. Fyodorov Eye Microsurgery Federal State Institution, Irkutsk, ivanov.andrei.med@yandex.ru, https://orcid.org/0009-0001-4235-9252

Eremina Alena V. – Cand. Sci. (Med.), Novosibirsk branch of S. Fyodorov Eye Microsurgery Federal State Institution, Novosibirsk, sci@mntk.nsk.ru, https://orcid.org/0000-0002-6913-0925

Trunov Aleksandr N. – Dr. Sci. (Med.), Professor, Novosibirsk branch of S. Fyodorov Eye Microsurgery Federal State Institution, Novosibirsk, trunov1963@yandex.ru, https://orcid.org/0000-0002-7592-8984

Chernykh Valeriy V. – Dr. Sci. (Med.), Professor, Novosibirsk branch of S. Fyodorov Eye Microsurgery Federal State Institution, Novosibirsk, sci@mntk.nsk.ru, https://orcid.org/0000-0002-7623-3359

(✉) **Konenkov Vladimir I.,** vikonenkov@gmail.com

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