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Effect of TXNRD2 rs35934224, FOXC1 rs2745599 and rs984253 genetic polymorphisms combinations on the development of primary open-angle glaucoma and their degree of association with the disease

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Primary open-angle glaucoma (POAG) is a complex disease caused by numerous genetic and environmental factors, as well as their interaction. In recent studies, the effect of genetic polymorphisms combinations and non-equilibrium linkage of allele genes related to the development of POAG has been proved. The aim of the study was to determine the effect of TXNRD2 rs35934224, FOXC1 rs2745599 and rs984253 genetic polymorphisms combinations on the development of primary open-angle glaucoma and their degree of association with the disease. The study included 93 patients (185 eyes) with POAG stage I-IV and 89 volunteers (178 eyes) control subjects without any types of glaucoma. The patients were divided into four groups according to the degree of perimetric changes (Nesterov A. P., 2008). All patients performed visometry, computer perimetry, tonometry, biomicroscopy, ophthalmoscopy, gonioscopy, keratophakymetry, optical coherent tomography of the optic nerve. Analysis of the TXNRD2 rs35934224, FOXC1 rs2745599 and rs984253 genetic polymorphism with POAG was performed in real time using a polymerase chain reaction (PCR) in Gene Amp® PCR System 7500 (Applied Biosystems, USA) automatic amplifier. In the first stage of the study, the genomic DNA from whole venous blood was isolated using the standard reagents PureLink® Genomic DNA Kit for purification of genomic DNA, manufactured by INVITROGEN (USA). The analysis of polymorphism was carried out using unified test systems of TaqMan Mutation Detection Assays Life-Technology (USA). It was determined that the association with POAG had the genotype C/T*A/A*T/A as by comparing control with all patients, and by stratification - with the 1st, 2nd and 3rd groups of patients. The obtained results showed the evidentiary effect of this genotype combinations on the appearance of POAG, and on its progression by the stages of perimetric changes. The risk of the occurrence of POAG in carriers of genotypes C/T*A/A*T/A was increased by 2.8 times ($p < 0.001$). In this combination, the two polymorphisms had heterozygous genotypes (rs35934224 - C/T, rs984253 - T/A), and the genotype rs2745599 - a mutant homozygote A/A. A combination of genotypes C/C*G/A*T/A was also important for the progression of the disease till stage II, which increased the risk of development of the POAG stage II by 2.9 times ($p < 0.01$) compared to control. The risk of occurrence of the POAG in general and development of stage IV increased the presence of combinations of three minor genotypes T/T*A/A*A/A, which was encountered only in patients with POAG (in stage II - $f = 0.025$, in the third stage - $f = 0.036$, and in IV - $f = 0.071$). In our opinion, it confirmed the proposed working hypothesis of the study and showed that the more genotype combinations have the mutant alleles, the stronger this genotype affects the development of POAG.

Keywords: primary open-angle glaucoma, chromosome, genotype, polymorphism, TXNRD2 gene, FOXC1 gene, allele, heterozygote.

Introduction

Primary open-angle glaucoma (POAG) is a complex disease caused by the combined effects of many genetic

and environmental risk factors, each of which do not act alone to cause glaucoma. Recent advances in molecular

genetics have shown that POAG can be caused by numerous gene mutations in various chromosomal loci. A study performed by Cong G. et al. estimated that inherited and familial POAG cases may account for approximately 72% of all POAG cases [6, 7, 8, 22, 27].

Another gene for testing as the genetic marker of the primary open-angle glaucoma (POAG) has become the developmental gene: forkhead box C1 (FOXC1) [1, 28]. This gene plays an important role in the normal morphogenesis of the anterior segment of the eye and is involved in the regulation of intraocular pressure and the function of the trabecular mesh [21]. The FOXC1 gene (previously FKHL7) is one of the six known genes of glaucoma [28]. Although FOXC1 expression has not been studied in adults yet, it is possible that prolonging the expression of an abnormal gene product (from age-related, sub-clinical mutations) throughout life, or altering the expression level of FOXC1 may affect the normal function of the trabecular mesh, thereby leading to an increased risk for the development of POAG through difficulty in drainage and increased intraocular pressure [26].

Another gene that has attracted our attention is the TXNRD2 gene encoding the mitochondrial protein, thioredoxin reductase 2, which is required for mitochondrial redox homeostasis. Thioredoxin 2 reduces the damaging effect of active forms of oxygen, which are formed as a result of oxidative phosphorylation [4]. And the decrease in the number of active forms of oxygen by activating the expression of the TXNRD2 gene prevents mitochondrial dysfunction and apoptosis of ganglion cells in POAG [1, 2].

In recent proceedings devoted to genetic research in the POAG [1, 21], the effects of combinations of polymorphic genotypes and non-equilibrium linkage of allele genes related to the development of POAG were considered. This approach is a very promising area of research, since a particular patient has a certain common genotype consisting of the specific polymorphic genotypes combinations.

That is why, in our opinion, when conducting studies of several polymorphic genes it is advisable to consider the association of genotype combinations with the development of the disease.

The aim of the study was to determine the effect of TXNRD2 rs35934224, FOXC1 rs2745599 and rs984253 genetic polymorphisms combinations on the development of primary open-angle glaucoma and their degree of association with the disease.

Materials and methods

The research was performed at the Department of Eye Diseases of the National Pirogov Memorial Medical University and the department of ophthalmology of Vinnitsa Regional Clinical Hospital Named After N. I. Pirogov. The examination of patients and the diagnosis of POAG was carried out in accordance with the classification of A. P. Nesterov perimetric changes in the stages of glaucoma [17].

The study included 93 patients (185 eyes) with POAG stage I-IV and 89 volunteers (178 eyes) control subjects

without any types of glaucoma. The patients were divided into four groups according to the degree of perimetric changes [17]. All patients performed visometry, computer perimetry, tonometry, biomicroscopy, ophthalmoscopy, gonioscopy, keratophymetry, optical coherent tomography of the optic nerve.

All stages of molecular genetic research were carried out at the Research Institute of Experimental and Clinical Medicine of the O. O. Bogomolets National Medical University (chief - m.d., professor Natrus L.V.). Analysis of the TXNRD2 rs35934224, FOXC1 rs2745599 and rs984253 genetic polymorphism with POAG was performed in real time using a polymerase chain reaction (PCR) in Gene Amp® PCR System 7500 (Applied Biosystems, USA) automatic amplifier. In the first stage of the study, the genomic DNA from whole venous blood was isolated using the standard reagents PureLink® Genomic DNA Kit for purification of genomic DNA, manufactured by INVITROGEN (USA). The analysis of polymorphism was carried out using unified test systems of TaqMan Mutation Detection Assays Life-Technology (USA). For statistical analysis of the results, MedStat and MedCalc v.15.1 (MedCalc Software bvba) were used. Association of genotypes and alleles with the disease were determined by the odds ratio (OR); The limits of 95% of the credible interval (CI) were calculated by the method of J. Neyman. The differences were statistically significant at $p < 0.05$. To test the probability of differences between groups, χ^2 was used and Fischer's exact criterion was used.

Results

The association with the disease has been confirmed only for genotype combinations C/C*A/A*T/A. It was shown that this genotype was found in the control group with a frequency of $f = 0.101$, and with POAG - with frequency $f = 0.238$, that is, 2.4 times more often ($p < 0.001$).

The genotype combinations C/C*A/A*T/A increased the chances of development of the POAG compared to the control by 2.8 times (OR = 2.775; 95% CI = 1.532-5.021). Also, the genotype combinations of T/T*A/A*A/A increased the risk of development POAG ($p < 0.05$), since such genotype wasn't detected in the control group. It should be noted that this genotype is a combination of all three mutant homozygotes. This fact confirmed the negative effect of the mutant alleles of all three polymorphisms on the occurrence of POAG.

According to the Table 1, four genotype combinations C/C*A/A*T/T, C/C*G/A*T/T, C/C*G/G*T/T and C/T*G/A*T/T showed a strong protective effect on POAG and substantially reduced the chances of development POAG.

The maximum power of connection was determined to genotype combinations C/C*G/G*T/T, which reduced the chances of development POAG by 7.7 times (OR = 0.132; 95% CI = 0.044-0.338). The genotype combinations C/T*G/A*T/T reduced the chances by 6.7 times (OR = 0.157; 95% CI = 0.035-0.697) and the genotype combinations C/C*A/A*T/T and C/C*G/A*T/T - 3.8 times for both cases (OR = 0.263; 95% CI = 0.101-0.685).

Table 1. Influence of genotype combinations on the development of POAG and their degree of association with the disease.

Genotypes	POAG	Control	χ^2	P	OR	95% CI
C/C*A/A*T/A	0.242	0.103	11.03	<0.001	2.775	1.532-5.021
C/C*A/A*T/T	0.033	0.111	7.552	<0.01	0.263	0.101-0.685
C/C*G/A*T/T	0.033	0.111	7.552	<0.01	0.263	0.101-0.685
C/C*G/G*T/T	0.024	0.152	16.93	<0.001	0.132	0.044-0.383
C/T*G/A*T/T	0.015	0.073	6.392	<0.05	0.157	0.035-0.697
T/T*A/A*A/A	0.031	0.001	4.044	<0.05	max	N/A-max

Notes: χ^2 - Pearson's χ -square criterion; p - statistical significance; OR - odds ratio; 95% CI - 95% credible interval for OR.

Fig. 1. Distribution of frequencies of genotype combinations in the control group and in patients with POAG when stratified in groups. The diagram shows genotype combinations for which the statistical significance of the differences at level $p < 0.05$ in the groups of comparisons was found, as well as the associative relation with the disease ($OR > 0$) according to the tables 1 and 2.**Table 2.** Influence of genotype combinations on the development of POAG and the degree of their association with disease in groups of patients.

Genotypes	Group	Control	χ^2	P	OR	95% CI	
	1st group						
C/C*A/A*T/A		0.488	0.103	18.86	<0.001	8.086	3.025-21.65
	2nd group						
C/C*A/A*T/A		0.224	0.103	5.852	<0.05	2.541	1.244-5.197
C/C*G/A*T/A		0.201	0.086	6.564	<0.01	2.885	1.336-6.243
C/C*G/A*T/T		0.025	0.111	4.434	<0.05	0.203	0.052-0.886
C/C*G/G*T/T		0.027	0.152	7.295	<0.01	0.154	0.033-0.642
	3rd group						
C/T*A/A*T/A		0.181	0.065	6.933	<0.01	3.735	1.464-9.524
C/C*G/G*T/T		0.042	0.152	3.884	<0.05	0.223	0.051-0.965
	4th group						
T/T*A/A*A/A		0.075	0.001	6.483	<0.05	max	N/A-max

Notes: χ^2 - Pearson's χ -square criterion; p - statistical significance; OR - odds ratio; 95% CI - 95% credible interval for OR

In this regard, at the next stage, the character of the distribution (Fig. 1) and the connection (Table 2) of the genotype combinations with POAG in stratification by groups was determined.

Among the risk genotypes, association with the disease has been confirmed only for genotype combinations C/C*A/A*T/A. It was shown above that this genotype was found in the control group with a frequency $f = 0.101$, and in POAG - with frequency $f = 0.238$, that is, 2.4 times more often ($p < 0.001$).

Henceforward, the nature of the connection between the genotype combinations with the disease when stratified by groups was calculated (Table 2).

In the 1st group, as in all patients with POAG, the association with the disease was determined only for genotype combinations C/C*A/A*T/A ($\chi^2 = 18.86$; $p < 0.001$), which in 8, 1 times increased the chances of development POAG (OR = 8,086; 95% CI = 3,025-21,65).

In the 2nd group, the genotype combinations C/C*A/A*T/A ($\chi^2 = 5.852$, $p < 0.05$) increased the chances of development POAG by 2.5 times (OR = 2.541; 95% CI = 1.244-5.197) as well as the genotype combinations C/C*G/A*T/A ($\chi^2 = 6.564$; $p < 0.01$), which increased the chances by 2.9 times (OR = 2.885; 95% CI = 1.336-6.243).

Two other genotype combinations, which in the 2nd group had a statistically significant association with POAG, reduced the chances of its development: C/C*G/G*T/T ($\chi^2 = 7.295$; $p < 0.01$) in 6,7 times (OR = 0.154; 95% CI = 0.033-0.642) and C/C*G/A*T/T ($\chi^2 = 4.434$; $p < 0.05$) - 5.0 times (OR = 0.203; 95% CI = 0.052-0.886).

In the 3rd group, reasonable differences were found for the risk genotype combinations C/T*A/A*T/A ($\chi^2 = 6.933$; $p < 0.01$), which increased the chances of development POAG by 3.7 times (OR = 3.735; 95% CI = 1.464-9.524) and for the protective genotype combinations C/C*G/G*T/T ($\chi^2 = 3.884$; $p < 0.05$), which reduced the chances of development POAG by 4,5 times (OR = 0,223; 95% CI = 0.051-0.965).

In the 4th group, the potentiating action of the combination of three mutant genotypes T/T*A/A*A/A ($\chi^2 = 6.483$; $p < 0.05$) was shown, which increased the chances of development POAG.

Discussion

Although increased intraocular pressure (IOP) is a key risk factor for primary open-angle glaucoma, the fact that about one third of European-born patients with glaucoma have a normal intraocular pressure (normotensive glaucoma) suggests that other factors may also affect the propensity to degeneration of optic nerve [9, 20]

There are increasing evidences of mitochondrial dysfunction in the susceptibility of the optic nerve to glaucoma [1, 5, 12, 14, 19, 23]. The retinal ganglion cell axons don't have a myelin sheath, so that sufficient amount of adenosine triphosphate (ATP) to maintain the potency of action in the absence of myelin is provided by a sufficient number of mitochondria. The optic nerve is a site that is particularly

susceptible to mitochondrial dysfunction [3, 13].

Genetic studies have shown that nuclear genes encoding mitochondrial proteins may contribute to the risk of COPD [10]. Recently, a large association of genomic studies revealed a significant association of POAG with single nucleotide polymorphism (SNPs) in the genomic region of *TXNRD2*, a nuclear-coded mitochondrial protein [1].

In previous studies, we determined the association of the *rs35934224* polymorphism of the *TXNRD2* gene with primary open-angle glaucoma. It was found that the polymorphism *rs35934224* had differences in the distribution of genotypes and alleles between patients with POAG and control group. Moreover, the shift of alleles and genotypes toward minor causes increased severity of the pathological process. But the stratification of the perimeter changes in the POAG showed that the association with the disease was significant at stages III and IV. Moreover, the chances of development of the III stage of POAG were significantly higher in comparison with the I stage in carriers of *C/T* and *T/T* genotypes and allele *T*. In the same plan, the protective effect of the ancestral genotype *C/C* was also strengthened [15].

FOXC1 is a gene that regulates the development of the anterior segment of the eye and is known to play a role in several autosomal dominant eye defects associated with increased risk of glaucoma, including the Axenfeld-Rieger anomaly, iris hypoplasia and Rieger syndrome [16, 18].

Foxc1 is expressed in the embryonic trabecular meshwork (TM) [25], the continuation of the expression of an abnormal gene product (from age-related, sub-clinical mutations) throughout life, or altered expression levels of *FOXC1* may affect the normal function of the trabecular meshwork, thereby leading to an increased risk of glaucoma due to increased intraocular pressure. This concept is confirmed by the fact that glaucoma associated with mutations in the genes of glaucoma development may occur at any time from birth to adulthood, and in some cases more than 70 years [24]. Moreover, in some patients with glaucoma due to *FOXC1* mutations, the anomalies of the anterior segment can be very thin and easily passed through a clinical examination [11, 24], which is more consistent with POAG.

The connection of the polymorphism of the *FOXC1* gene to the development of POAG has been studied in individual studies. Thus, in a study by British scientists [21] four polymorphisms were studied: *rs2235715*, *rs2569889*, *rs2235716* and *rs984253*. In this case, all these polymorphisms do not cling to the coding region of the gene, and only the latter is located in the non-coding intron of the *FOXC1* gene (16 13 294). We conducted a study of the association of polymorphisms *rs984253* and *rs2745599* of the *FOXC1* gene with POAG. In which it was discovered that the distribution of genotypes and alleles had a relationship with POAG, but polymorphism *rs984253* had no relation to its progression in the stages of the pathological process. While the polymorphism *rs2745599*

of the *FOXC1* gene was related to the formation of the POAG of the most severe (IV) degree, and the risk of rapid progression of the disease was greater in the carriers of the minor allele *A*.

In this study, we determined the effects of the combinations of genotypes of polymorphisms on the development of POAG and the degree of their association with the disease. We found that the association with the disease had the genotype *C/T*A/A*T/A* as a comparison of control with all patients, and with stratification - from the 1st, 2nd and 3rd groups of patients. In our opinion, this convincingly indicated the evidentiary effect of this combination of genotypes and on the occurrence of POAG, and on its progression in the stages of perimetric changes. The risk of occurrence of POAGs in carriers of *C/T*A/A*T/A* genotypes was increased by 2.8 times ($p < 0.001$). Interestingly, in this combination, the two polymorphisms had heterozygous genotypes (*rs35934224* - *C/T*, *rs984253* - *T/A*), and the genotype *rs2745599* was a mutant homozygote *A/A*.

A combination of *C/C*G/A*T/A* genotypes was also important for the progression of the disease to stage II, which increased the risk of developing the II stage of POAG by 2.9 times ($p < 0.01$) compared to control.

The risk of both general POAG and stage IV development increased the presence of combinations of three minor *T/T*A/A*A/A* genotypes that were found only in patients with POAG (at stage II $f = 0.025$, in stage III - $f = 0.036$, and for IV - $f = 0.071$). In our opinion, this testified in favor of the proposed working hypothesis of the study and confirmed that the more combined the genotypes of the mutant alleles, the stronger this genotype affects the development of POAG.

Conclusions

1. The association with the disease had the genotype *C/T*A/A*T/A* as a comparison of control with all patients, and with stratification - with the 1st, 2nd and 3rd groups of patients. The risk of the occurrence of POAG in carriers of *C/T*A/A*T/A* genotypes was increased by 2.8 times (OR = 2.775; 95% CI = 1.532-5.021). Also, the combination of minor *T/T*A/A*A/A* genotypes made a significant increase in the risk of development of POAG ($p < 0.05$), since no such genotype was detected in the control group.

2. For the progression of the disease to the II stage, the combination of *C/C*G/A*T/A* genotypes was also important, which increased the risk of development of the II stage of POAG in 2.9 times ($p < 0.01$) as compared with the control.

3. The probable protective effect on the POAG was determined to combine the genotypes *C/C*G/G*T/T*, which reduced the chances of development of the POAG by 7.7 times (OR = 0.132; 95% CI = 0.044-0.383). The combination of genotypes *C/T*G/A*T/T* reduced the chances by 6.7 times (OR = 0.157; 95% CI = 0.035-0.697) and the combination of genotypes *C/C*A/A*T/T* and *C/C*G/A*T/T* - 3.8 times for both cases (OR = 0.263; 95% CI = 0.101-0.685).

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ВПЛИВ СПОЛУЧЕНЬ ГЕНОТИПІВ ПОЛІМОРФІЗМІВ RS35934224 ГЕНА TXNRD2, RS2745599 І RS984253 ГЕНА FOXC1 НА РОЗВИТОК ПЕРВИННОЇ ВІДКРИТОКУТОВОЇ ГЛАУКОМИ І СТУПІНЬ ЇХ АСОЦІАЦІЇ З ЗАХВОРЮВАННЯМ

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Первинна відкритокутова глаукома (ПВКГ) - це складне захворювання, викликане численними генетичними й екологічними факторами, а також їх взаємодією. У останніх наукових дослідженнях було доведено вплив сполучень поліморфних генотипів та нерівноважне зчеплення алелів генів, що мають відношення до розвитку ПВКГ. Мета дослідження - визначення впливу

сполучень генотипів поліморфізмів rs35934224 гена TXNRD2, rs2745599 і rs984253 гена FOXC1 на розвиток ПБКГ і ступінь їх асоціації з захворюванням. Проведено дослідження 93 хворих (185 очей) з ПБКГ I-IV стадій та 89 добровольців (178 очей), у яких не було встановлено будь-якої глаукоми, що склали контрольну групу. Хворих було розподілено на 4 групи відповідно до ступеня периметричних змін (Nesterov A. P., 2008). Всім хворим виконано візометрію, комп'ютерну периметрію, тонометрію, біомікроскопію, офтальмоскопію, гоніоскопію, кератопахиметрію, оптичну когерентну томографію зорового нерва. Аналіз поліморфізмів rs35934224 гена TXNRD2, rs2745599 і rs984253 гена FOXC1 проведено методом полімеразної ланцюгової реакції у реальному часі в автоматичному ампліфікаторі Gene Amp® PCR System 7500 (Applied Biosystems, США). На першому етапі дослідження проводили виділення геномної ДНК з цільної венозної крові з використанням стандартних реактивів PureLink® Genomic DNA Kit For purification of genomic DNA, виробник INVITROGEN (США). Аналіз поліморфізму здійснено з використанням уніфікованих тест-систем TaqMan Mutation Detection Assays Life-Technology (США). Встановлено, що асоціацію з ПБКГ має генотип С/Т*А/А*Т/А як при порівнянні контролю зі всіма хворими, так і при стратифікації - з 1-ю, 2-ю і 3-ю групами хворих. Отримані результати свідчать про доказовий вплив цього сполучення генотипів і на виникнення ПБКГ, і на її прогресування за стадіями периметричних змін. Ризик виникнення ПБКГ у носіїв сполучення генотипів С/Т*А/А*Т/А збільшено у 2,8 рази ($p < 0,001$). У цьому сполученні два поліморфізми мали гетерозиготні генотипи (rs35934224 - С/Т, rs984253 - Т/А), а генотип rs2745599 - мутантну гомозиготу А/А. Для прогресування захворювання до II стадії мало значення також сполучення генотипів С/С*Г/А*Т/А, яке збільшує ризик розвитку II стадії ПБКГ у 2,9 рази ($p < 0,01$) у порівнянні з контролем. Ризик як загалом ПБКГ, так і розвитку IV стадії підвищувала наявність сполучень трьох мінорних генотипів Т/Т*А/А*А/А, яке зустрічалося тільки у хворих на ПБКГ (при II стадії $f=0,025$, при III стадії $f=0,036$, а при IV - $f=0,071$). На наш погляд, це свідчило на користь висунутої робочої гіпотези дослідження та підтвердило, що чим більше у сполученні генотипів мутантних алелів, тим сильніше такий генотип впливає на розвиток ПБКГ.

Ключові слова: первинна відкритокутова глаукома, хромосома, генотип, поліморфізм, ген TXNRD2, ген FOXC1, алель, гетерозигота.

ВЛИЯНИЕ СОЕДИНЕНИЙ ГЕНОТИПОВ ПОЛИМОРФИЗМОВ RS35934224 ГЕНА TXNRD2, RS2745599 И RS984253 ГЕНА FOXC1 НА РАЗВИТИЕ ПЕРВИЧНОЙ ОТКРЫТОУГОЛЬНОЙ ГЛАУКОМЫ И СТЕПЕНЬ ИХ АССОЦИИАЦИИ С ЗАБОЛЕВАНИЕМ

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Первичная открытоугольная глаукома (ПОУГ) - это сложное заболевание, вызванное многочисленными генетическими и экологическими факторами, а также их взаимодействием. В последних научных исследованиях было доказано влияние соединений полиморфных генотипов и неравновесное сцепление аллелей генов, имеющих отношение к развитию ПОУГ. Цель исследования - определение влияния соединений генотипов полиморфизмов rs35934224 гена TXNRD2, rs2745599 и rs984253 гена FOXC1 на развитие ПОУГ и степень их ассоциации с заболеванием. Проведено исследование 93 больных (185 глаз) с ПОУГ I-IV стадий и 89 добровольцев (178 глаз), у которых не было установлено какой-либо глаукомы, составивших контрольную группу. Больные были разделены на 4 группы согласно степени периметрических изменений (Nesterov A. P., 2008). Всем больным выполнена визометрия, компьютерная периметрия, тонометрия, биомикроскопия, офтальмоскопия, гониоскопия, кератопахиметрия, оптическая когерентная томография зрительного нерва. Анализ полиморфизмов rs35934224 гена TXNRD2, rs2745599 и rs984253 гена FOXC1 проведено методом полимеразной цепной реакции в реальном времени в автоматическом амплификаторе Gene Amp® PCR System 7500 (Applied Biosystems, США). На первом этапе исследования проводили выделение геномной ДНК из цельной венозной крови с использованием стандартных реактивов PureLink® Genomic DNA Kit For purification of genomic DNA, производитель INVITROGEN (США). Анализ полиморфизма осуществлено с использованием унифицированных тест-систем TaqMan Mutation Detection Assays Life-Technology (США). Установлено, что ассоциации с ПОУГ имел генотип С/Т*А/А*Т/А как при сравнении контроля со всеми больными, так и при стратификации - с 1-й, 2-й и 3-й группами больных. Полученные результаты свидетельствуют о доказательном влиянии этого соединения генотипов и на возникновение ПОУГ, и на ее прогрессирование по стадиям периметрических изменений. Риск возникновения ПОУГ у носителей соединений генотипов С/Т*А/А*Т/А увеличен в 2,8 раза ($p < 0,001$). В этом сочетании два полиморфизма имели гетерозиготные генотипы (rs35934224 - С / Т, rs984253 - Т/А), а генотип rs2745599 - мутантную гомозиготу А/А. Для прогрессирования заболевания до II стадии имело значение также соединение генотипов С/С*Г/А*Т/А, которое увеличивает риск развития II стадии ПОУГ в 2,9 раз ($p < 0,01$) по сравнению с контролем. Риск как в целом ПОУГ, так и развития IV стадии повышалось наличие соединения трех мінорных генотипов Т/Т*А/А*А/А, которое встречалось только у больных ПОУГ (при II стадии $f = 0,025$, при III стадии - $f = 0,036$, а при IV - $f = 0,071$). На наш взгляд, это свидетельствовало в пользу выдвинутой рабочей гипотезы исследования и подтвердило, что чем больше в соединении генотипов мутантных аллелей, тем сильнее такой генотип влияет на развитие ПОУГ.

Ключевые слова: первичная открытоугольная глаукома, хромосома, генотип, полиморфизм, ген TXNRD2, ген FOXC1, аллель, гетерозигота.