Primary open-angle glaucoma (POAG) is a complex disorder. Genetic factors play a vital part in POAG. The prevalence of POAG is gender-specific: the disorder is more often diagnosed in women. Results of the genome-wide association studies (GWAS) strongly support the association of CDKN2B-AS1 gene polymorphism with POAG. The aim was to perform the replicative study of CDKN2B-AS1 gene polymorphic loci association with POAG in women of the Central Black Earth Region, Russia. Five CDKN2B-AS1 gene single nucleotide polymorphisms (SNPs), rs1063192, rs7865618, rs2157719, rs944800, and rs4977756, were genotyped in 290 female patients with POAG and 220 female controls. The differences in the haplotype block structure between the POAG patients (no haplotype block) and the controls (haplotype block consisting of three SNPs, rs1063192, rs7865618 and rs2157719) was detected. The CDKN2B-AS1 gene haplotype GGG rs1063192–rs7865618–rs2157719 is associated with POAG in women. This haplotype is considered a protective factor of the disorder (OR = 0.66, p = 0.006, \( \rho_{\text{corr}} = 0.037 \)).

**Keywords:** primary open-angle glaucoma, CDKN2B-AS1, polymorphism, associations, women

**Author contribution:** Eliseeva NV — sample design, molecular genetic testing, manuscript writing; Ponomarenko IV — molecular genetic testing, statistical analysis, manuscript writing; Churnosov MI — study concept, manuscript editing; the final version of the manuscript was read and approved by all authors.

**Compliance with ethical standards:** the study was approved by the Ethics Committee of the Institute of Medicine of the Belgorod State University (protocol № 4 dated May 19, 2015); the informed consent to participation was submitted by all study participants.

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**ORIGINAL RESEARCH | GENETICS**

**CDKN2B-AS1 GENE POLYMORPHISM IS ASSOCIATED WITH PRIMARY OPEN-ANGLE GLAUCOMA IN WOMEN OF THE CENTRAL BLACK EARTH REGION, RUSSIA**

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Glaucoma is a disorder characterized by chronic, progressive optic neuropathy associated with changes in optic nerve head and retinal nerve fiber morphology, which are not attributed to other eye disorders or congenital malformations [1]. Primary open angle glaucoma (POAG) is one of the most common forms of glaucoma [2]. The data on the stable sustained incidence rate growth, chronic disease with progressive visual impairment, resulting ultimately in the loss of working ability and disability, demonstrate the sociomedical significance of glaucoma [1]. It should be noted that in the vast majority of cases POAG is diagnosed in patients aged 60–69, commonly having systemic comorbidities. The disorder is almost 1.5 times more often diagnosed in women [1–3].

**Genetic factors play a significant role in POAG [4].** Molecular genetic data received to date suggest the involvement of a number of candidate gene polymorphisms in POAG [4–6]. Several genome-wide studies (GWAS) of POAG revealed associations of CDKN2B-AS1 polymorphic loci with the disorder [7–12]. CDKN2B-AS1 gene is located within the chromosome 9p21 CDKN2B–CDKN2A gene cluster. CDKN2B-AS1 belongs to the group of genes responsible for regulation of the long non-coding RNA (IncRNA) synthesis [13]. IncRNA encoded by the gene interacts with polycomb repressive complex-1 (PRC1) and -2 (PRC2), which results in significant epigenetic alterations (histone methylation and monoubiquitination, etc.). This, in
result, results in significant structural changes of chromatin and directly affects the expression of genes [13]. It should be noted that GWAS data on POAG require replicative studies in various populations, such as Russian population, which have not been subject to replicative studies to date.

The study was aimed to assess the association of the CDKN2B-AS1 gene single nucleotide polymorphism (SNP) with POAG in women of the Central Black Earth Region, Russia.

METHODS

The sample included 290 female patients with POAG and 220 female controls. Inclusion criteria: Russian ethnicity, place of birth and residence — Central Black Earth Region of Russia [14]. Exclusion criteria: non-Russian ethnicity, place of birth and/or residence — outside the Central Black Earth Region of Russia.

The group of patients included individuals diagnosed with POAG, their diagnosis was verified based on the clinical and instrumental examination data. POAG was diagnosed based on the following criteria [6]: elevated intraocular pressure (IOP over 21 when measured by pneumotonometer), glaucomatous optic nerve excavation, characteristic changes in the peripheral visual field. The control group included individuals having no POAG (IOP below 21 when measured by pneumotonometer, and below 25 when measured by Maklakov tonometry, no glaucomatous optic nerve excavation and characteristic changes in the peripheral visual field), other eye disorder or severe somatic comorbidity rate (> 0.05) (Table 1). Ophthalmic instrumental examination was carried out in the specialized department of the St. Ioasaph Belgorod Regional Clinical Hospital.

Genomic DNA obtained from peripheral venous blood with phenol–chloroform extraction was subject to genetic analysis [15]. CDKN2B-AS1 gene single nucleotide polymorphism was selected for analysis based on the following criteria [16]: 1) association with POAG according to previous genome-wide studies; 2) significant regulatory potential; 3) minor allele frequency of 5% or greater.

SNPs were selected for analysis using the catalog of human genome-wide association studies (GWAS Catalog) [17] and the HaploReg database [18]. Five CDKN2B-AS1 gene SNPs were included in the study: rs1063192, rs7865618, rs2157719, rs944800, and rs4977756. All five SNPs were associated with POAG based on the previous GWAS data [7–12], had a significant regulatory potential (rs7865618, rs2157719, rs944800 are located within the region of histone modifications defined as enhancer marks; rs1063192, rs2157719, rs944800, rs4977756 are located within the DNase I hypersensitive sites; rs1063192, rs2157719, rs944800 are located within the region of various transcription factors regulatory DNA elements), and their minor allele frequency exceeded 5%.

DNA samples were genotyped with the CFX96 Real-Time PCR detection system (Bio-Rad; USA) using the TaqMan probes and the tailor-made kits (TestGene; Russia).

Associations of polymorphic loci with POAG were assessed using logistic regression analysis within the framework of allele (for rs1063192, rs7865618, rs2157719, and rs4977756 polymorphisms alleles G vs. A with a minor allele G were analyzed, and for rs944800 locus it was A vs. G with a minor allele A), dominant (for rs1063192, rs7865618, rs2157719, and rs4977756 polymorphisms alleles G vs. A with a minor allele A), recessive (for rs1063192, rs7865618, rs2157719, and rs4977756 polymorphisms alleles A vs. G with a minor allele G), additive (G/G vs. G/A vs. A/A were analyzed; for rs944800 A/A + G/A vs. G/G were analyzed), and for multiple comparisons (permutation testing was applied to adjust the results for multiple comparisons. P<perm value < 0.05 was considered statistically significant).

Lewontin’s standardized disequilibrium coefficient (D’) and Pearson correlation coefficient (r2) were used for assessment of linkage disequilibrium and haplotype block identification between five CDKN2B-AS1 gene SNPs. Haplotype blocks were analyzed with the Haplovip v.4.2 software [20] using the Solid Spine algorithm with D’ > 0.8. Visualization of linkage disequilibrium between studied CDKN2B-AS1 SNPs was performed using the Haplovip v. 4.2 software. Haplotype frequencies were estimated using the EM algorithm. Associations of haplotypes with POAG were assessed using logistic regression analysis with the plink 1.06 software; the data were adjusted for covariate (age) and for multiple comparisons (permutation testing was applied — 1000 permutations). Evaluation of haplotype association with the disorder was performed using odds ratio (OR). P<perm value < 0.05 was considered statistically significant [21].

RESULTS

Population genetic analysis showed that distribution of all five CDKN2B-AS1 SNP genotypes in POAG patients and controls satisfied the Hardy–Weinberg equilibrium (pHWE > 0.05) (Table 2).

Table 1. Biomedical and clinical anamnestic characteristics of the studied groups

| Parameters                  | Patients (n = 290) | Controls (n = 220) | ρ       |
|-----------------------------|-------------------|-------------------|---------|
| Age, years                  | 62.24 ± 11.45     | 61.78 ± 11.06     | 0.45    |
| BMI, kg/m²                  | 28.72 ± 5.19      | 28.57 ± 5.49      | 0.78    |
| Somatic comorbidities, % (n) |                   |                   |         |
| Cardiovascular system       | 80.69 (234)       | 74.55 (164)       | 0.12    |
| Endocrine system            | 20.34 (59)        | 15.91 (35)        | 0.24    |
| Gastrointestinal tract      | 14.14 (41)        | 12.73 (28)        | 0.74    |
| Urinary tract               | 7.58 (22)         | 7.27 (16)         | 0.99    |
| Respiratory tract           | 6.55 (19)         | 5.45 (12)         | 0.74    |
| Nervous system              | 18.28 (53)        | 17.27 (38)        | 0.86    |
| Other                       | 3.45 (10)         | 3.16 (7)          | 1       |

Note: ρ values were calculated using permutation testing.
No significant associations of studied polymorphic CDKN2B-AS1 loci with POAG were revealed in women (Table 3).

Analysis of linkage disequilibrium between five studied CDKN2B-AS1 gene polymorphisms using the Solid Spine algorithm ($D' > 0.8$) revealed no haplotype blocks in women with POAG. However, a haplotype block comprising three polymorphisms, rs1063192, rs7865618, and rs2157719, was identified in controls (see Figure). Furthermore, information reported in Figure indicates the existence of recombination hotspots between loci rs2157719 and rs944800 with quite low degree of genetic linkage between rs944800 and rs4977756, as well as high degree of linkage between loci rs4977756 and three polymorphisms (rs1063192, rs7865618 and rs2157719), in the control group. Furthermore, while in the control group there is a zone with $D'$ value about 0.4 (see above), then among patients the $D'$ value for all studied polymorphisms is about 0.6–0.7.

Association of GGG haplotype of the identified CDKN2B-AS1 haplotype block rs1063192–rs7865618–rs2157719 with POAG in women was defined. The OR value calculated for this haplotype was 0.66 ($p = 0.006$ and $p_{\text{perm}} = 0.037$), which demonstrated the protective effect of the haplotype against the disorder in women (Table 4). Association of AGA haplotype with POAG (OR $= 5.12$; $p = 0.009$) did not reach statistical significance based on the permutation testing results ($p_{\text{perm}} = 0.06$).

**DISCUSSION**

Comparison of patients with POAG and female controls based on five CDKN2B-AS1 gene SNPs revealed the differences in linkage disequilibrium between the studied loci (low degree on genetic linkage between distinct loci in the control group with a $D'$ value of about 0.4, and almost “uniform” linkage of all studied genetic linkage between distinct loci in the control group with a high degree on five loci). Furthermore, while in the control group there is a zone with $D'$ value about 0.4 (see above), then among patients the $D'$ value for all studied polymorphisms is about 0.6–0.7, and the related differences in haplotype block structure (when using the Solid Spine algorithm with $D' > 0.8$), no haplotype blocks were identified in POAG patients, however, in female controls, haplotype block comprising three SNPs, rs1063192, rs7865618 and rs2157719, was identified. Association of GGG haplotype of CDKN2B-AS1 gene rs1063192–rs7865618–rs2157719 with POAG in women (OR $= 0.66$) together with no significant independent associations of five studied CDKN2B-AS1 gene SNPs with the disorder were detected.

It is believed that linkage disequilibrium patterns in modern populations are the result of evolution, which reflects both the demographic history of the population (migration, population subdivision, etc.), and the gene-specific factors, related to mutation and recombination rates, selection, etc. [22]. Despite the fact that the use of LD structure for studying the complex human disorders is limited by the population specificity [22], it is believed that the use of haplotypes for association studies instead of distinct SNPs makes it possible to significantly improve the statistical power of the study, especially where the disease susceptibility loci are not analyzed directly, or in case of high degree multilocus linkage disequilibrium [22, 23]. Genetic distance between the studied loci and the “causative” mutation, as well as allele frequency and the “causative” mutation age, has a direct impact on the haplotype testing efficiency [22].

Regardless of the fact that no obvious “causative” mutations for POAG (for example, nonsense mutations or mutations associated with amino acid substitution) have been detected within the chromosomal region comprising the studied CDKN2B-AS1 gene SNPs to date, a number of papers report high functional significance of polymorphic loci located within the region (effect on the expression of CDKN2A, CDKN2B, etc.) [8, 12].

Linkage disequilibrium features detected and related features of haplotype block identification between five studied CDKN2B-AS1 SNPs in the control group may be just a “particular case” of haplotype structure at the “local scale” of population history and genetic structure, as well as allele frequency and the “causative” mutation age, has a direct impact on the haplotype testing efficiency [22].

Regardless of the fact that no obvious “causative” mutations for POAG (for example, nonsense mutations or mutations associated with amino acid substitution) have been detected within the chromosomal region comprising the studied CDKN2B-AS1 gene SNPs to date, a number of papers report high functional significance of polymorphic loci located within the region (effect on the expression of CDKN2A, CDKN2B, etc.) [8, 12].

**Table 2. Distribution of CDKN2B-AS1 gene polymorphic loci in POAG patients and female controls**

| Polymorphism | Rare allele | Frequent allele | Rare allele frequency | Number of studied chromosomes | Genotype distribution, proportion (%) (homozygous/heterozygous/homozygous for a rare allele) | Observed heterozygosity | Expected heterozygosity | Significance level for deviations from Hardy–Weinberg equilibrium ($p_{\text{obs}}$) |
|--------------|-------------|----------------|----------------------|-------------------------------|------------------------------------------------|-----------------------|------------------------|-----------------------------------------------|
| rs1063192    | G           | A              | 0.423                | 568                           | 53/134/97 (18.66/47.18/34.16)                         | 0.472                 | 0.488                  | 0.627                                      |
| rs7865618    | G           | A              | 0.417                | 566                           | 52/132/99 (18.45/46.64/34.96)                         | 0.466                 | 0.486                  | 0.541                                      |
| rs2157719    | G           | A              | 0.385                | 564                           | 45/127/110 (15.96/45.03/39.01)                        | 0.450                 | 0.473                  | 0.450                                      |
| rs944800     | A           | G              | 0.338                | 574                           | 32/130/125 (11.15/45.30/43.55)                        | 0.453                 | 0.448                  | 0.896                                      |
| rs4977756    | G           | A              | 0.476                | 572                           | 61/150/75 (21.33/52.45/26.22)                         | 0.525                 | 0.499                  | 0.409                                      |

POAG patients ($n = 290$)

Control group ($n = 220$)

| Polymorphism | Rare allele | Frequent allele | Rare allele frequency | Number of studied chromosomes | Genotype distribution, proportion (%) (homozygous/heterozygous/homozygous for a rare allele) | Observed heterozygosity | Expected heterozygosity | Significance level for deviations from Hardy–Weinberg equilibrium ($p_{\text{obs}}$) |
|--------------|-------------|----------------|----------------------|-------------------------------|------------------------------------------------|-----------------------|------------------------|-----------------------------------------------|
| rs1063192    | G           | A              | 0.46                 | 424                           | 43/109/60 (20.28/51.42/28.30)                        | 0.514                 | 0.497                  | 0.679                                      |
| rs7865618    | G           | A              | 0.463                | 436                           | 47/108/63 (21.56/49.54/28.90)                        | 0.495                 | 0.497                  | 1.000                                      |
| rs2157719    | G           | A              | 0.429                | 438                           | 41/106/72 (18.72/48.40/32.88)                        | 0.484                 | 0.490                  | 0.890                                      |
| rs944800     | A           | G              | 0.368                | 440                           | 28/106/66 (12.73/48.18/39.09)                        | 0.482                 | 0.465                  | 0.665                                      |
| rs4977756    | G           | A              | 0.459                | 438                           | 46/109/64 (21.01/49.77/29.22)                        | 0.498                 | 0.497                  | 1.000                                      |
Table 3. Association of CDKN2B-AS1 gene polymorphism with POAG in women

| Loci      | Alleles, genotypes                  | Patients, n (%) | Controls, n (%) | OR (95% CI)   | p     |
|-----------|-------------------------------------|----------------|----------------|---------------|-------|
| rs1063192 | G vs. A (allele model)              | 240/328 (42.25/57.75) | 195/229 (45.99/54.01) | 0.86 (0.67–1.11) | 0.24  |
|           | G/G vs. A/G vs. A/A (additive model) | 53/134/97 (18.66/47.18/34.16) | 43/109/60 (20.28/51.42/28.30) | 0.82 (0.61–1.10) | 0.2   |
|           | G/G vs. A/G vs. A/A (additive model) | 187/97 (65.84/34.16) | 152/60 (71.10/28.30) | 0.69 (0.44–1.08) | 0.1   |
|           | G/G vs. A/G + A/A (recessive model) | 53/233 (18.66/61.34) | 43/169 (20.28/78.72) | 0.90 (0.54–1.50) | 0.66  |
| rs7865618 | G vs. A (allele model)              | 236/330 (41.70/58.30) | 202/234 (46.33/53.67) | 0.83 (0.64–1.07) | 0.14  |
|           | G/G vs. A/G vs. A/A (additive model) | 52/132/99 (18.38/46.64/34.96) | 47/108/63 (21.56/49.54/28.90) | 0.89 (0.67–1.19) | 0.43  |
|           | G/G vs. A/G vs. A/A (additive model) | 184/99 (65.02/34.98) | 155/63 (71.10/28.90) | 0.74 (0.47–1.15) | 0.18  |
|           | G/G vs. A/G + A/A (recessive model) | 52/231 (18.38/81.62) | 47/171 (21.56/78.44) | 1.05 (0.63–1.75) | 0.85  |
| rs2157719 | G vs. A (allele model)              | 217/347 (45.30/54.70) | 182/256 (42.92/57.08) | 0.84 (0.64–1.07) | 0.15  |
|           | G/G vs. A/G vs. A/A (additive model) | 45/127/110 (15.96/45.03/39.01) | 41/106/72 (18.72/48.40/32.88) | 0.87 (0.65–1.16) | 0.34  |
|           | G/G vs. A/G vs. A/A (additive model) | 172/110 (60.99/39.01) | 147/72 (67.12/32.88) | 0.74 (0.48–1.16) | 0.19  |
|           | G/G vs. A/G + A/A (recessive model) | 45/237 (15.96/64.04) | 41/178 (18.72/81.28) | 0.97 (0.56–1.66) | 0.91  |
| rs9448000 | A vs. G (allele model)              | 194/380 (33.80/66.20) | 162/278 (36.82/63.18) | 0.88 (0.67–1.14) | 0.32  |
|           | A/A vs. G/A vs. G/G (additive model) | 32/130/125 (11.15/45.30/43.55) | 28/106/66 (12.73/48.18/39.09) | 0.80 (0.59–1.08) | 0.15  |
|           | A/A vs. G/A vs. G/G (additive model) | 162/125 (56.45/43.55) | 134/86 (60.91/39.09) | 0.75 (0.49–1.14) | 0.18  |
|           | A/A vs. G/A + G/G (recessive model) | 32/255 (11.15/68.85) | 28/192 (12.73/87.27) | 0.74 (0.40–1.37) | 0.34  |
| rs4977756 | G vs. A (allele model)              | 272/300 (47.55/52.45) | 201/237 (45.89/54.11) | 1.07 (0.83–1.37) | 0.6   |
|           | G/G vs. A/G vs. A/A (additive model) | 61/150/75 (21.33/52.45/26.22) | 46/108/64 (21.01/49.77/29.22) | 1.11 (0.82–1.49) | 0.5   |
|           | G/G vs. A/G vs. A/A (additive model) | 211/75 (73.78/26.22) | 155/64 (70.78/29.22) | 1.22 (0.76–1.93) | 0.41  |
|           | G/G vs. A/G + A/A (recessive model) | 61/225 (21.33/78.67) | 46/173 (21.01/78.99) | 1.07 (0.64–1.76) | 0.81  |

Note: Results were obtained using the logistic regression model; OR — odds ratio, 95% CI — 95% confidence interval (lower and upper bound of 95% CI); p — significance level.
Association of CDKN2B-AS1 gene loci with glaucoma/endophenotypes

Black Earth Region, Russia (OR = 0.66), are consistent with the data of previous studies.

During the previous studies the following data were obtained for CDKN2B-AS1 gene allele G rs7865618 being a part of the GGG haplotype of haplotype block rs1063192–rs7865618–rs2157719, which, according to our data, is considered a protective factor of POAG in women of the European Russia (OR = 0.66). According to GWAS [8], allele A rs7865618 increases the risk of POAG in Japanese population (OR = 1.56; \( p = 2 \times 10^{-3} \)); according to genome-wide studies [29, 30], CDKN2B-AS1 gene allele G rs7865618 is associated with smaller optic nerve vertical cup-to-disc ratio (\( \beta = -0.013; \ p = 3 \times 10^{-35} \) for European population) [29] and smaller area of excavation (\( \beta = -0.023; \ p = 1 \times 10^{-31} \) in total for European and Asian populations) [30]. Thus, it is worth noting that our data and the existing literature data on the protective effect of CDKN2B-AS1 gene allele G rs7865618 against POAG and pathogenetically significant signs of POAG (optic nerve vertical cup-to-disc ratio, area of excavation) fit together.

According to literary sources, CDKN2B-AS1 gene allele G rs2157719 is associated with low risk of POAG in ethnically diverse populations (in Asian population, in Europeans, and African Americans) [11, 12] and smaller optic nerve vertical cup-to-disc ratio (\( \beta = -0.013; \ p = 4 \times 10^{-35} \) in total for European and Asian populations) [30]. These data are consistent with our results: allele G rs2157719 being a part of GGG haplotype of haplotype block rs1063192–rs7865618–rs2157719 is considered a protective factor of POAG in women of the European Russia (OR = 0.66).

Despite the fact that a number of GWAS have shown significant associations of CDKN2B gene SNPs with glaucoma and related endophenotypes (optic nerve vertical cup-to-disc ratio, area of excavation) [7–12, 25–30], the results of replicative studies performed in various populations are often uncertain, and, in a number of cases, inconsistent, as meta-analysis [28] has shown (CDKN2B-AS1 polymorphism rs1063192 was analyzed). A number of studies have confirmed association of CDKN2B-AS1 gene loci with glaucoma/endophenotypes related to glaucoma (optic nerve vertical cup-to-disc ratio) [26, 28, 31, 32]; other studies have revealed no associations of individual CDKN2B-AS1 gene SNPs with the disorder (for example, rs1063192 and rs4977756 are not associated with POAG in the Indian population [33], in African Americans [34], and in the Pakistan population [35]). The ambiguity of the results obtained by studying the CDKN2B-AS1 gene loci association with glaucoma are clearly demonstrated by the paper issued in 2021 [33] on meta-analysis of several CDKN2B-AS1 gene SNPs, including rs1063192, rs2157719 and rs4977756, which were used in our study: thus, of 18 association studies included in the meta-analysis (among them six studies of POAG in Caucasians), significant associations of rs1063192 with POAG have been shown only in 10 studies; significant associations of rs2157719 with POAG have been shown in three of five studies subjected to analysis; only four of 12 papers report significant associations of rs4977756 with the disorder. The study [34], which showed significant association with POAG only in one locus of African Americans out of 24 studied loci (the sample included 1150 patients and 999 controls), can be consider another good example of ambiguous data on association of CDKN2B-AS1 SNPs with glaucoma: none of these 24 SNPs were associated with the disorder in the population of west Africa (the sample included 483 patients and 593 controls). Significant independent associations of five CDKN2B-AS1 gene SNPs with POAG have not been revealed during our study as well.

Such ambiguity of the results may be due to clinical heterogeneity of the studied samples of patients, as well as to the differences in the ethnic makeup of the studied populations. Other possible explanations for the ambiguity of association study results are as follows: unique external factors (environmental factors, lifestyle, etc.) in the distinct ethnographic groups, the prevalence of various complex disorders contributing to glaucoma заболеваний (atherosclerosis, diabetes mellitus, coronary heart disease, etc.) in these groups [1], as well as the range of environmental glaucoma risk factors related to the listed reasons, which is taken or not taken into account by the researchers during their studies.

Regardless of the fact that the distinct “major” effects of the studied CDKN2B-AS1 gene loci on POAG in women has not been defined, it has been shown that the combination of certain alleles of the three studied CDKN2B-AS1 gene SNPs (GGG rs1063192–rs7865618–rs2157719) in the haplotype defines susceptibility to POAG in women of the Central Black Earth Region, Russia. The vital role of the CDKN2B-AS1 gene haplotypes in susceptibility to POAG has been also shown in the Indian population [33]: CATA haplotype rs3217992–rs1063192–rs2157719–rs4977756 increased the risk of the disorder by 1.61 times (\( p \leq 0.0001 \)), however, the Bonferroni adjusted distinct effects of the listed loci were not statistically significant. It can be assumed, in case of several “risk” CDKN2B-AS1 gene alleles in the genotype their regulatory effects [8, 12] add up and overcome some threshold essential for glaucoma susceptibility formation in the population, which was tested during our study.

Table 4. Association of CDKN2B-AS1 gene polymorphic loci rs1063192–rs7865618–rs2157719 haplotypes with POAG in women

| Haplotype | Haplotype frequency | OR | p |
|-----------|---------------------|----|----|
|           | Patients (n = 290)  |     |    |
| GGG       | 0.287               | 0.66| 0.006|
| AGG       | 0.03                | 2.22| 0.075|
| GAG       | 0.026               | 2.87| 0.127|
| AAG       | 0.039               | 1.92| 0.145|
| GGA       | 0.066               | 1.43| 0.321|
| AGA       | 0.031               | 5.12| 0.009|
| GAA       | 0.045               | 1.67| 0.215|
| AAA       | 0.475               | 0.9 | 0.483|
|           | Controls (n = 220)  |     |    |
| GGG       | 0.377               |     |    |
| AGG       | 0.021               |     |    |
| GAG       | 0.008               |     |    |
| AAG       | 0.023               |     |    |
| GGA       | 0.049               |     |    |
| AGA       | 0.014               |     |    |
| GAA       | 0.033               |     |    |
| AAA       | 0.475               |     |    |

Note: Results were obtained using the logistic regression model; OR — odds ratio; \( p \) — significance level.
CONCLUSION

The data obtained using the Solid Spine algorithm ($D' > 0.8$) indicate the differences in haplotype blocks for five studied \textit{CDKN2B-AS1} gene SNPs between patients with POAG (no haplotype blocks) and controls (haplotype block was identified consisting of three SNPs: rs1063192, rs7865618, and rs2157719). Association of \textit{CDKN2B-AS1} gene GGG haplotype (rs1063192-rs7865618-rs2157719) with POAG in women of the Central Black Earth Region, Russia, has been defined. This haplotype is considered a protective factor for the development of the disorder (OR = 0.66; $p = 0.006$, $p_{perm} = 0.037$).

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