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HUMAN GENETICS

Analysis of Associations of Polymorphic Loci of the *LOXL1* Gene with the Development of Primary Open-Angle Glaucoma in Women of the Central Chernozem Region of Russia

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Abstract—A replicative study of associations of the *LOXL1* gene polymorphism with primary open-angle glaucoma (POAG) in the female population of the Central Chernozem region of Russia was performed. The work was done in the design "patients–control." The study sample consisted of 290 women with POAG and 220 women in the control group. Three polymorphic loci of the *LOXL1* gene (rs2165241, rs4886776, rs893818) were genotyped by PCR (Tag-Man probe technology). The study revealed that SNPs of the *LOXL1* gene (rs2165241, rs4886776, rs893818) are associated with POAG in women of the Central Chernozem region of Russia: allele *C* of rs2165241 (OR = 0.33–0.45 at $p_{perm} \le 0.0005$), alleles *A* of rs4886776 (OR = 0.62–0.63 at $p_{perm} \le 0.031$) and rs893818 (OR = 0.53–0.62 at $p_{perm} \le 0.007$), and the CAA haplotype of rs2165241–rs4886776–rs893818 (OR = 0.56 at $p_{perm} = 0.022$) are protective for the development of the disease, and the TGG haplotype (OR = 2.19 at $p_{perm} = 0.001$) is associated with an increased risk of developing POAG in women.

Keywords: *LOXL1*, associations, primary open-angle glaucoma, polymorphism, women

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INTRODUCTION

Glaucoma is a group of heterogeneous neurodegenerative diseases with common pathogenetic pathways, which are based on the progressive loss of retinal ganglion cells and optic nerve axons, leading to visual field defects [1]. Epidemiological studies show that worldwide 64.3 million people aged 40–80 years suffer from glaucoma and, according to scientists, the prevalence of the disease will increase to 111.8 million in 2040 [1]. Primary open-angle glaucoma (POAG) is the most common form of glaucoma, which is one of the main causes of blindness worldwide [2, 3]. It should be noted that POAG occurs most often among women and somewhat less frequently among men [2, 3].

According to the literature, genetic factors play an important role in the development of glaucoma [4, 5]. Genome-wide association studies (GWAS) have identified a number of candidate genes associated with glaucoma, including the lysyl oxidase-like enzyme gene (*LOXL1*) [6–8]. The product of gene *LOXL1* modulates biogenesis of the extracellular matrix by crosslinking elastin and collagen in connective tissues [9]. Elastin is the main component of elastic fibers of the extracellular matrix of the ethmoid plate, and deformation of the ethmoid plate can damage the axons of retinal ganglion cells [9]. The relationship of a number of polymorphic loci of the gene *LOXL1* to the level of its expression has been shown [8, 10].

It is important to note that until recently it was believed that polymorphism of gene *LOXL1* was associated only with pseudoexfoliative syndrome/pseudoexfoliative glaucoma (PES/PEG) and was not associated with the development of other types of glaucoma (POAG, primary angle-closure glaucoma, pigmentary glaucoma) [11]. However, in recent years, data have appeared on the association of polymorphism of gene *LOXL1* with POAG [12], including in genome-wide studies [7].

The objective is a replicative study of the associations of polymorphism of gene *LOXL1* with POAG in the female population of the Central Black Earth region of Russia.

MATERIALS AND METHODS

The sample for the study was represented by 510 women, of which 290 were patients with POAG and 220 were the control group. A specialized examination was carried out at the clinical base of the Department of Ophthalmosurgery of the Belgorod Regional Clinical Hospital. All patients with POAG and individuals in the control group gave written informed consent to participate in the study.

The group of patients included individuals with a diagnosis of POAG, which was verified as a result of clinical and clinical and instrumental examination of patients. POAG was diagnosed on the basis of appropriate criteria—high intraocular pressure (IOP above 21 with pneumotonometry and above 25 with Maklakov tonometry), glaucomatous excavation of the optic nerve head, and characteristic changes in the peripheral visual field [13]. Among patients with POAG, cardiovascular diseases were found in 72.76%, diseases of the endocrine system in 15.86%, nervous system in 14.83%, digestive system in 12.07%, reproductive system in 11.03%, and urinary system in 7.24%. The control group included individuals who did not have POAG (IOP below 21 with pneumotonometry and below 25 with Maklakov tonometry, absence of glaucomatous excavation of the optic nerve head and characteristic changes in the peripheral visual field), other eye diseases, or severe concomitant somatic pathology accompanied by eye damage [14]. The studied samples of patients and controls included unrelated individuals of Russian nationality born and living in the Central Black Earth region of Russia [15, 16]. The age of POAG patients and the control group did not differ significantly (62.24 ± 11.45 and 61.78 ± 11.06 years, respectively, with $p > 0.05$).

Genomic DNA (isolated from venous blood samples by phenol/chloroform extraction method) was used as an object for experimental research [17]. For molecular genetic research, selection of polymorphic loci of the gene *LOXL1* was based on the following criteria [18, 19]: (1) associations with glaucoma according to the results of previous genome-wide studies; (2) the presence of regulatory potential and relationship to gene expression [20]; (3) the frequency of the minor allele of 5% or more.

The SNPs were selected using the Genome-Wide Research Directory (GWAS) (http://www.genome.gov/gwastudies/) and the database HaploReg (http://archive.broadinstitute.org/mammals/haploreg/). According to the above criteria, three polymorphic loci of gene *LOXL1* (rs2165241, rs4886776, rs893818) were selected for this study. All three polymorphisms were associated with glaucoma (exfoliative glaucoma/syndrome) according to GWAS data [6, 8, 21, 22], had significant regulatory potential, and were associated with expression of genes; the frequency of minor alleles exceeded 5%.

For genotyping SNPs, we used the polymerase chain reaction method (Tag-Man probe technology) and locus-specific kits developed and synthesized by Test-Gen LLC (Ulyanovsk). Experimental studies were carried out on a CFX96 amplifier (manufactured by Bio-Rad) according to the manufacturer's protocol.

To analyze the associations of polymorphic loci and their haplotypes with POAG, we used the logistic regression method [23, 24], implemented in the plink 1.06 program (freely available on the electronic resource http://pngu.mgh.harvard.edu/Èpurcell/plink). The calculations were performed within the framework of the dominant, additive, and recessive genetic models [25]. Linkage mismatch of SNPs of gene *LOXL1* was estimated on the basis of the Lewontin (D') and Pearson (r^2) coefficients. To assess the nature of the association, the odds ratio (OR) and its 95% interval (95% CI) were used [26]. The calculations were corrected for multiple comparisons (an adaptive permutation procedure was performed) and covariates (age). The indicator was taken as statistically significant $p_{perm} < 0.05$ [27].

RESULTS AND DISCUSSION

For all three polymorphic loci of gene *LOXL1* (rs2165241, rs4886776, rs893818) studied, both among patients and in the control in the distribution of genotypes (observed and expected), Hardy–Weinberg equilibrium was performed (taking into account the Bonferroni correction for the number of analyzed loci, $n = 3$, $p_{bonf} > 0.017$) (Table 1). The incidence of minor (rare) allelic variants was higher than 17%.

The associations of the studied polymorphic loci of gene *LOXL1* (rs2165241, rs4886776 and rs893818) with the development of POAG in women were established (Table 2). The rs2165241 polymorphism is associated with POAG in all three analyzed genetic models: additive—OR = 0.45 ($p = 7.55 \times 10^{-7}$, $p_{perm} = 1.00 \times 10^{-6}$), dominant—OR = 0.37 ($p = 6.46 \times 10^{-6}$, $p_{perm} = 7.00 \times 10^{-6}$), and recessive—OR = 0.33 ($p = 0.0004$, $p_{perm} = 0.0005$). Polymorphic loci rs4886776 and rs893818 are associated with the development of the disease in women according to the additive (OR = 0.62, $p = 0.012$, $p_{perm} = 0.015$ and OR = 0.62, $p = 0.008$, $p_{perm} = 0.007$, respectively) and dominant (OR = 0.63, $p = 0.032$, $p_{perm} = 0.031$ and OR = 0.53, $p = 0.004$, $p_{perm} = 0.004$, respectively) genetic models. It should be noted that all alternative variants of these polymorphic loci (allele *C* of rs2165241, alleles *A* of rs4886776 and rs893818) are protective for the development of the disease (OR < 1).

It was revealed that the three studied polymorphisms of gene *LOXL1* (rs2165241, rs4886776, rs893818) are located nearby (the physical distance between them is 6000 bp), are in a state of linkage disequilibrium ($r^2 = 0.31–0.72$, $D' = 0.78–0.87$), and form a single haploblock. Associations with POAG formation in women of three haplotypes rs2165241–rs4886776–rs893818 of gene *LOXL1* were determined (Table 3): TGG (OR = 2.19, $p = 2 \times 10^{-6}$, $p_{perm} = 0.001$), CGG (OR = 0.44, $p = 0.0001$, $p_{perm} = 0.002$), CAA (OR = 0.56, $p = 0.006$, $p_{perm} = 0.022$).

Our results are consistent with published data on this issue. In the first genome-wide study of glaucoma performed in 2007 by G. Thorleifsson et al. [8] in the populations of Iceland and Sweden, the study

Table 1. Characterization of the distribution of polymorphic loci of gene *LOXL1* among patients with POAG and women in the control group

Polymorphism	Rare allele	Frequent allele	Rare allele frequency	Number of studied chromosomes	Data on the distribution of genotypes, number (%)*	Observed heterozygosity (H_o)	Expected heterozygosity (H_e)	p_{HWE}
Patients with POAG (n = 290)								
rs2165241	*C*	*T*	0.276	576	24/111/153 (8.33/38.54/53.13)	0.385	0.400	0.556
rs4886776	*A*	*G*	0.189	572	4/100/182 (1.39/34.97/63.64)	0.350	0.306	0.019
rs893818	*A*	*G*	0.176	568	9/82/193 (3.17/28.87/67.96)	0.289	0.290	1.000
Control group (n = 220)								
rs2165241	*C*	*T*	0.461	438	45/112/62 (20.55/51.14/28.31)	0.511	0.497	0.786
rs4886776	*A*	*G*	0.271	432	15/87/114 (6.94/40.28/52.78)	0.403	0.395	0.864
rs893818	*A*	*G*	0.259	432	14/84/118 (6.48/38.89/54.63)	0.389	0.384	1.000

* Data are shown in the format of homozygote for a rare allele/heterozygote/homozygote for a frequent allele.

Table 2. Polymorphism associations of gene *LOXL1* with POAG in women

SNP	Alleles, genotypes	Patients, *n* (%)	Control, *n* (%)	OR (95% CI)	*p*
rs2165241	Sample size	288	219		
	C vs. *T* (allelic model)	159/417 (27.60/72.40)	202/236 (46.12/53.88)	0.45 (0.34–0.58)	1.06E-09
	C/C vs. *T/C* vs. *T/T* (additive model)	24/111/153 (8.33/38.54/53.13)	45/112/62 (20.55/51.14/28.31)	0.45 (0.33–0.62)	7.55E-7
	C/C + *T/C* vs. *T/T* (dominant model)	135/153 (46.87/53.13)	157/62 (71.69/28.31)	0.37 (0.24–0.57)	6.46E-6
	C/C vs. *T/C* + *T/T* (recessive pattern)	24/264 (8.33/91.67)	45/174 (20.55/79.45)	0.33 (0.18–0.61)	0.004
rs4886776	Sampling size	286	216		
	A vs *G* (allelic model)	108/464 (18.88/81.12)	117/315 (27.08/72.92)	0.63 (0.47–0.84)	0.02
	A/A vs. *G/A* vs. *G/G* (additive model)	4/100/182 (1.39/34.97/63.64)	15/87/114 (6.94/40.28/52.78)	0.62 (0.43–0.90)	0.012
	A/A + *G/A* vs. *G/G* (dominant model)	104/182 (36.36/63.64)	102/114 (47.22/52.78)	0.63 (0.41–0.96)	0.032
	A/A vs. *G/A* + *G/G* (recessive model)	4/282 (1.39/98.61)	15/201 (6.94/93.06)	0.30 (0.09–1.03)	0.056
rs893818	Sampling size	284	216		
	A vs. *G* (allelic model)	100/468 (17.61/82.39)	112/320 (25.93/74.07)	0.61 (0.45–0.83)	0.001
	A/A vs. *G/A* vs. *G/G* (additive model)	9/82/193 (3.17/28.87/67.96)	14/84/118 (6.48/38.89/54.63)	0.62 (0.43–0.88)	0.008
	A/A + *G/A* vs. *G/G* (dominant model)	91/193 (32.04/67.96)	98/118 (45.37/54.63)	0.53 (0.35–0.82)	0.004
	A/A vs. *G/A* + *G/G* (recessive model)	9/275 (3.17/96.83)	14/202 (6.48/93.52)	0.69 (0.26–1.87)	0.469

The results were obtained by the method of logistic regression; OR—odds ratio, 95% CI—95% confidence interval; *p*—the level of statistical significance.

Table 3. Haplotype associations of polymorphic loci of *LOXL1* with POAG in women

Haplotype	Haplotype frequency		OR	*p*
	patients ($n = 290$)	control ($n = 220$)		
CAA	0.143	0.206	0.56	0.006
TAA	0.012	0.028	0.48	0.24
CGA	0.011	0.013	0.83	0.809
TGA	0.010	0.009	2.74	0.197
CAG	0.015	0.017	1.51	0.533
TAG	0.019	0.020	1.44	0.536
CGG	0.110	0.227	0.44	0.0001
TGG	0.680	0.480	2.19	2.00E-06

The results were obtained by the method of logistic regression; OR—odds ratio; *p*—the level of statistical significance.

included 274 patients with PEG, 290 patients with POAG (thus, the total sample of patients with glaucoma was 564 people), and 14672 people in the control group. The authors established the associations of rs2165241 of gene *LOXL1* with development as PEG (OR = 3.62, $p = 1.00 \times 10^{-27}$) and glaucoma in general (combined sample of PEG and POAG) (OR = 1.96, $p = 1.30 \times 10^{-16}$).

A significant role of rs2165241 polymorphism of gene *LOXL1* in the formation of pseudoexfoliative syndrome without glaucoma was shown in a genome-wide study by K. Zagajewska et al. [21] in the Polish population (the work was performed on a sample of 209 individuals, including 103 patients and 106 in the control group). The authors found that the minor allele *C* is a protective factor in the development of PES (OR = 0.24), while the reference allele for it *T* significantly increases the risk of developing the disease (OR = 4.2, $p = 2.77 \times 10^{-10}$).

It should be noted that our data are fully consistent with the results of the earlier study by V. Zanon-Moreno et al. [12] in the Spanish population. In this work (a genetic study of 232 patients with POAG and 241 in the control group), it was found that the polymorphism rs2165241 of gene *LOXL1*, which previously showed, as the authors note, associations with pseudoexfoliative glaucoma, is also associated with the development of POAG in the Mediterranean population, and, as for PEG, allele *T* of rs2165241 of gene *LOXL1* (according to the recessive genetic model for *TT* versus *CC*, OR = 2.19, 95% CI 1.33–3.62, corrected for age and weight OR = 2.07, 95% CI 1.20–3.57) increases the risk of developing POAG.

A significant role of the allele *T* of rs2165241 as a risk factor for PES/PEG has been shown in studies of the Latin American population [28], German and Italian populations [29], residents of Spain [30], and other populations [31–33]. The meta-analysis results presented by J.Z. Tang et al. [34] indicate the protective significance of the genotype *CC* of rs2165241 in the formation of pseudoexfoliative syndrome/glaucoma.

It should be noted that polymorphic variants of the rs2165241 locus of gene *LOXL1* have a multidirectional nature of associations with the development of the disease in populations of different ethnic composition. So, if in European populations, as established in the works cited above [8, 21, 29], the risk factor for the development of PES/PEG is the allele *T* of rs2165241, then in Asian populations the risk factor for the development of the disease is the allele *C* of rs2165241 [29, 35]. It should also be noted that, in European populations, as a rule, the allele *T* of rs2165241 is frequent, and in Asian populations, the allele *C* of rs2165241 is frequent [12, 21, 35].

The relationship of the SNP rs893818 of gene *LOXL1* considered in our work to PEG at a genome-wide level of statistical significance was first discovered in 2014 by the research team of M. Nakato et al. [6] when studying the population of Japan. Associations with PES of rs4886776 of gene *LOXL1* was first demonstrated in the GWAS study by T. Aung et al. [22]. At the same time, it should be noted that, in this work, oppositely directed associations of rs4886776 of *LOXL1* with PES in populations with different ethnic composition: allelic variant *A* of rs4886776 is a risk factor for PES in the Japanese population (OR = 9.87, $p = 2.35 \times 10^{-217}$) and what was, as the authors point out in their work, a "surprise" for them serves as a protective factor for PES in non-Japanese populations (including Caucasians) (OR = 0.49, $p = 2.35 \times 10^{-317}$). These data are fully consistent with the results obtained in our work—in the studied population of Russia (Caucasian population), protective a factor in the development of POAG is the allele *A* of rs4886776 of gene *LOXL1* (OR = 0.63). The multidirectional nature of the association of another polymorphism of gene *LOXL1* (rs4886778) with the development of pseudoexfoliative syndrome was identified in the work of F. Pasutto et al. [29]: in the Italian and German populations, the risk factor for the development of the

disease is the allele *C* of rs4886778 (OR = 3.95, $p = 1.54 \times 10^{-32}$ and OR = 3.10, $p = 8.30 \times 10^{-22}$ respectively), while in the Japanese population, the risk factor is the allele *A* (OR = 6.85, $p = 1.53 \times 10^{-136}$).

It should be noted that the single nucleotide polymorphic loci studied by us are located in the first intron of the gene *LOXL1*. These polymorphic variants, according to previously published data, modify the activity of the promoter region of the gene *LOXL1-AS1* [36], affect the binding of this DNA region to the RXRa transcription factor, and are involved in the processes of alternative splicing of gene *LOXL1* [29]. Gene *LOXL1-AS1* (*LOXL1 antisense RNA 1*) is a long noncoding RNA with significant regulatory effects [37]. Literature sources indicate engagement of *LOXL1-AS1* into the pathophysiology of pseudoexfoliative syndrome owing to participation in the cellular stress response, in which there is a significant dysregulation of the expression of this noncoding RNA [36]. Shown is a significant role for lncRNA *LOXL1-AS1* in modulation of the expression of genes responsible for the response to oxidative stress and degradation of the extracellular matrix involved in the formation of collagen structures (*HMOX1*, *TIMP3*, *LOXL4*, *ACTA2*, *COL6A3*, and others) and other genes that are "key" for the pathophysiology of glaucoma [38].

The data obtained indicate the involvement of polymorphic loci of gene *LOXL1* (rs2165241, rs4886776, rs893818) in the formation of POAG in women of the Central Black Earth region of Russia. Allelic variants *C* of rs2165241, *A* of rs4886776, and *A* of rs893818, as well as haplotype CAA of rs2165241–rs4886776–rs893818 exhibit a "protective" role in the formation of POAG in the female population of the Central Black Earth region of Russia, while the haplotype TGG, conversely, is associated with a higher risk of POAG.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interest. The authors declare that they have no conflict of interest.

Statement of compliance with standards of research involving humans as subjects. All procedures performed in a study involving people comply with the ethical standards of the institutional and/or national committee for research ethics and the 1964 Helsinki Declaration and its subsequent changes or comparable ethical standards.

Informed voluntary consent was obtained from each of the participants.

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