LOXL1 gene polymorphism candidates for exfoliation glaucoma are also associated with a risk for primary open-angle glaucoma in a Caucasian population from central Russia

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Purpose: This study was aimed to replicate the previously reported associations of the three *LOXL1* gene polymorphisms with exfoliation glaucoma (XFG) and to analyze these genetic variants for their possible contribution to primary open-angle glaucoma (POAG) in Caucasians from central Russia.

Methods: In total, 932 participants were recruited for the study, including 328 patients with XFG, 208 patients with POAG, and 396 controls. The participants were of Russian ethnicity (self-reported) and born in Central Russia. They were genotyped at three single nucleotide polymorphisms (SNPs) of the *LOXL1* gene (rs2165241, rs4886776, and rs893818). The association was analyzed using logistic regression.

Results: Allele C of rs2165241 was associated with a decreased risk of XFG (odds ratio [OR] $=0.27–0.45$, $p_{perm} \leq 5*10^{-6}$) and POAG (OR$=0.35–0.47$, $p_{perm} \leq 0.001$), and allele A of rs4886776 and rs893818 were associated with a lower risk of XFG (OR$=0.53–0.57$, $p_{perm} \leq 0.001$). Haplotype TGG of loci rs2165241-rs4886776-rs893818 was associated with an elevated risk of XFG (OR$=2.23$, $p_{perm}=0.001$) and POAG (OR$=2.01$, $p_{perm}=0.001$), haplotype CGG was also associated with a decreased risk of XFG (OR$=0.45$, $p_{perm}=0.001$) and POAG (OR$=0.35$, $p_{perm}=0.001$). Haplotype CAA was associated with a decreased risk of XFG only (OR$=0.50$, $p_{perm}=0.001$).

Conclusions: Polymorphisms rs2165241, rs4886776, and rs893818 of the *LOXL1* gene showed association with XFG and POAG in a Caucasian sample from central Russia.

Glaucoma is a group of heterogeneous disorders associated with the progressive degeneration of the optic nerve and consequently, impaired vision and blindness. The number of people 40–80 years worldwide diagnosed with this disease is estimated at more than 64 million and is projected to reach 111.8 million in 2040 [1]. Primary open-angle glaucoma (POAG) and secondary open-angle glaucoma due to exfoliation syndrome (XFG) are among the main causes of permanent blindness worldwide [2]. POAG is the most common type of glaucoma resulting from progressive optic neuropathy and visual field deterioration in eyes with gonioscopically open angles, often associated with elevated intraocular pressure [3]. XFG is the most common form of secondary glaucoma, characterized by abnormal deposition of protein in various anterior eye structures [4]. Compared to POAG, XFG is characterized by a higher mean intraocular pressure, a more significant loss of the visual field, and poorer treatment response [4].

Genetic factors apparently play a significant role in the development of glaucoma [5,6]. Several genome-wide association studies (GWASs) have suggested a group of genes, including the lysyl oxidase-like 1 (*LOXL1*) gene (GeneID: 4016, OMIM:153456), associated with XFG (rs893818, rs1048661, rs2165241) [7,8], and POAG (rs1048661) [9].

The product of the *LOXL1* gene links collagen and elastin in connective tissues and thus, contributes to the formation of the extracellular matrix [10]. Elastin makes up the elastic fibers in the extracellular matrix of the lamina cribrosa, and malformation of the lamina cribrosa results in damage of retinal ganglion cell axons [11]. As polymorphisms are reported to affect *LOXL1* expression [7,12], this may result in structural modifications of ganglion cells and their axons in the retina and subsequently, in the development of glaucoma.

Previously, it was thought that the *LOXL1* gene was associated only with XFG and had no relation to the other types of glaucoma (POAG, primary angle-closure glaucoma, pigmentary glaucoma) [6]. However, recent data suggested that this gene might be associated with POAG [9,13]. The present study was aimed to replicate the association of the three *LOXL1* gene polymorphisms with XFG and to analyze their possible association with POAG in a sample of Caucasians from central Russia.

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METHODS

Study subjects: In total, 932 participants, including 328 patients with XFG, 208 patients with POAG, and 396 controls were recruited for the study. When recruiting the participants, the following inclusion criteria were applied: Russian ethnicity (self-reported) and birthplace in central Russia [14]. The participants underwent a comprehensive ocular examination, which included slit-lamp, applanation tonometry, visual acuity test, an examination of the optic disc, and measurement of the central corneal thickness. XFG was diagnosed based on a) the presence of exfoliation deposits on the iris, lens capsule, or corneal endothelium and b) the presence of glaucomatous cupping of the optic disc, loss of the visual field, and intraocular pressure (IOP) ≥21 mmHg or controlled IOP on antiglaucomatous treatment in at least one eye. All participants underwent pupillary dilation to determine the presence of exfoliation deposits on the anterior lens capsule. POAG was diagnosed according to the criteria described elsewhere [15]: open angle of the anterior chamber, high intraocular pressure (≥21 mmHg), distinctive changes in the optic disc (e.g., notching, thinning of the neuroretinal rim at the vertical poles, increased excavation/optic disc ratio), glaucoma-specific defects of the visual field (arcuate or para-central scotoma, narrowing of the view field with the nose), and no exfoliation deposits on the lens capsule, iris, or corneal endothelium in either eye. Control subjects had no exfoliation material deposits on anterior segment structures, no diagnosis of POAG, constant IOP readings of <21 mmHg, normal optic discs, and no acute eye disease or any secondary injury to the eyes at the time of the examination.

All study participants signed an informed consent according to the principles of the Declaration of Helsinki and The Association for Research in Vision and Ophthalmology before enrollment in the study. The study protocol was approved by the Ethical Review Committee of Belgorod State University. The medical examination of the participants was conducted at the Department of Eye Microsurgery of St. Joasaph Belgorod Regional Clinical Hospital.

DNA isolation and genotyping assay: Blood (5 ml) was drawn by a certified nurse from the ulnar vein of each participant to a plastic vial (Vacutainer®, Warwick, RI) containing 0.5M EDTA solution (pH=8.0). Total genomic DNA was isolated from buffy coat using the standard phenol-chloroform method and then checked for quality using Nanodrop 2000 spectrophotometer (Thermo Scientific, Inc., Grand Island, NE). Only samples with A260/A280 = 1.7-2.0 were included in the analysis. The isolated DNA was stored at -80ºC ((as described previously by Ponomarenko et al. [16]).

Three single nucleotide polymorphisms (SNPs) of the *LOXL1* gene (rs2165241, rs4886776, rs893818) were selected for the analysis. The selection criteria were described elsewhere [17]: 1) previously reported associations with XFG/exfoliation syndrome (XFS) with GWASs (Appendix 1), 2) regulatory potential (Appendix 2), and 3) minor allele frequency (MAF) >5%. All the SNPs above had significant regulatory potential as determined using HaploReg (v4.1, update 05.11.2015) [18] (Appendix 2) and were associated with XFG/XFS in the previously published GWAS (Appendix 1).

The three SNPs of the *LOXL1* gene were genotyped with several other candidate polymorphisms for glaucoma (not selected for the present study) using the matrix assisted laser desorption ionization-time-of-flight (MALDI-TOF) mass spectrometry iPLEX platform (Agena Bioscience Inc., San Diego, CA). Blind replicates were genotyped to ensure quality control. The repeatability test conducted using 5% randomly selected samples yielded 100% reproducibility.

Statistical analysis: The correspondence of the determined allele and genotype frequencies to Hardy–Weinberg equilibrium (HWE) was estimated with the chi-square test. The logistic regression approach with adjustment for covariates was applied to analyze associations of the genetic variants with XFG and POAG. The three standard genetic models were assumed: additive, recessive, and dominant. The following covariates were applied: age, body mass index (BMI), systolic and diastolic blood pressures as quantitative variables and a family history of glaucoma, the presence of essential hypertension, heart atherosclerosis, heart ischemia, and diabetes mellitus (either type I or type II) as qualitative variables (Table 1). Adjustment for multiple comparisons for several SNPs was performed using the adaptive permutation test [19], and that for the number of genetic models (three) and groups compared (three), using the Bonferroni correction. Thus, the aggregated level of significance was set at p_{perm}<0.006 (0.05/9). Quanto 1.2.4 (Hydra 2009) was used to compute statistical power for each SNP.

The confidence intervals algorithm at D'>0.8 as implemented in HaploView v.4.2 was applied to identify haplotype blocks. Adjustment for multiple comparisons was performed using the permutation test (1,000 permutations). Taking account of the number of haplotypes studied (seven) and the number of cohorts (three), the aggregate significance level after the Bonferroni correction was set at p_{perm}<0.0024 (0.05/21). The computations above were performed using the respective algorithms implemented in the gPLINK v. 2.050 software.

TABLE 1. PHENOTYPIC CHARACTERISTICS OF THE STUDY PARTICIPANTS.

Parameters	Controls, mean ± SD, % (n)		XFG patients mean ± SD, % (n)	p	POAG patients mean ± SD, % (n)	p	P XFG - POAG
N	396	-	328	-	208	-	-
Age, years	62.02±11.54	<0.001	71.64±8.67	<0.001	69.80±8.61	<0.001	0.03
(min−max)	(42−87)		(43−94)		(46−87)		
Gender ratio, m/f	44.44/55.56 (176/220)	0.49	47.26/52.74 (155/173)	0.53	43.75/56.25 (91/117)	0.94	0.48
BMI, kg/m2	27.95±5.45	<0.001	27.57±4.69	0.53	28.42±5.09	0.18	0.05
Mean systolic blood pressure, mm Hg	130.87±14.83	<0.001	142.29±17.67	<0.001	139.64±16.01	<0.001	0.1
Mean diastolic blood pressure, mm Hg	84.08±9.57	<0.001	87.24±11.57	<0.001	83.89±9.27	0.36	<0.001
Smoke	28.03 (111)	0.58	25.91 (85)	0.58	26.92 (56)	0.85	0.88
Alcohol consumption	32.07 (127)	0.64	30.18 (99)	0.64	30.77 (64)	0.82	0.26
Family history of glaucoma	6.06 (24)	<0.001	20.12 (66)	<0.001	19.23 (40)	<0.001	0.88
Ophthalmological characteristics							
Intraocular pressure, mm Hg	16.41±1.54	<0.001	25.19±5.78	<0.001	25.12±5.86	<0.001	0.86
Cup to disc ratio	0.25±0.08	<0.001	0.72±0.31	<0.001	0.74±0.35	<0.001	0.78
Somatic pathologies							
Essential hypertension	61.11 (242)	0.002	72.56 (238)	0.002	67.79 (141)	0.13	0.29
Arterial hypotension	5.81 (23)	0.44	4.27 (14)	0.44	4.33 (9)	0.56	1
Heart atherosclerosis	14.14 (56)	<0.001	29.57 (97)	<0.001	39.90 (83)	<0.001	0.02
Heart ischemia	24.00 (95)	<0.001	35.36 (116)	<0.001	40.38 (84)	<0.001	0.28
Diabetes	10.10 (40)	0.05	15.24 (50)	0.05	17.31 (36)	0.02	0.6
Digestive system pathology	12.88 (51)	0.65	14.33 (47)	0.65	14.42 (30)	0.69	1
Kidney pathology	7.32 (29)	0.64	8.54 (28)	0.64	7.69 (16)	0.98	0.85
Respiratory system pathology	5.05 (20)	0.65	6.10 (20)	0.65	6.73 (14)	0.51	0.91
Nervous system pathology	9.09 (36)	0.97	9.45 (31)	0.97	10.09 (21)	0.8	0.92

P values <0.05 are shown in bold.

RESULTS

The phenotypic characteristics of the case (XFG and POAG) and control groups are presented in Table 1. The patients with XFG and POAG were older (p<0.001), had higher systolic and diastolic blood pressure (p<0.001), higher rates of family history of glaucoma (p<0.001), the presence of essential hypertension (p<0.001), heart atherosclerosis (p<0.001), heart ischemia (p<0.001), and diabetes (p≤0.05) compared to the controls (Table 1). The patients with POAG had higher BMI (p=0.05), higher rates of heart atherosclerosis (p=0.02), and lower diastolic blood pressure (p<0.001) compared to the patients with XFG (Table 1). Therefore, all the factors above were applied as covariates in the association analyses.

The data for the three polymorphisms are shown in Appendix 3. All SNPs had MAF >5% and no departure from the HWE (p>0.05). Variant rs2165241 was associated with XFG and POAG according to all genetic models (Table 2). Polymorphisms rs4886776 and rs893818 were associated only with XFG according to the additive and dominant models (Table 2).

Haplotype TGG was associated with an increased risk of XFG (OR=2.23, p_{perm}=0.001) and POAG (OR=2.01, p_{perm}=0.001), and haplotype CGG was associated with a decreased risk of XFG (OR=0.45, p_{perm}=0.001) and POAG (OR=0.35, p_{perm}=0.001; Table 3, Figure 1). In addition, haplotype CAA was associated with a decreased risk only of XFG (OR=0.50, p_{perm}=0.001; Table 3). The groups of patients with XFG and POAG did not differ by allele and haplotype frequencies.

DISCUSSION

LOXL1 polymorphisms, in particular rs2165241, have been extensively studied and documented for their association with XFG/XFS in different populations, including Caucasians [7,8,20-23], Asians [20,21,24], and others [25]. We found only one study reporting the association of the *LOXL1* polymorphism (rs2165241) with POAG in a Caucasian population [13]. Interestingly, the *LOXL1* allelic variants associated with glaucoma have a reversed, or "flip-flop," risk effect in Asian and Caucasian populations. Studies of Caucasian populations (including the present one) reported alleles T of rs2165241, G

TABLE 2. ASSOCIATIONS OF THE *LOXL1* GENE SNPs WITH XFG AND POAG.

Genetic models	SNP	Minor allele	n	OR	95%CI L95	95%CI U95	P	P_{perm}	Power
XFG									
Additive model	rs2165241	C	719	0.45	0.34	0.58	$2*10^{-9}$	$1*10^{-6}$	0.9999
	rs4886776	A	717	0.55	0.4	0.75	0.0002	0.0002	0.9945
	rs893818	A	710	0.57	0.42	0.77	0.0004	0.0004	0.9879
Dominant model	rs2165241	C	719	0.39	0.27	0.55	$1*10^{-7}$	$1*10^{-6}$	0.9999
	rs4886776	A	717	0.53	0.37	0.76	0.0005	0.0007	0.9829
	rs893818	A	710	0.55	0.38	0.78	0.001	0.001	0.9691
Recessive model	rs2165241	C	719	0.27	0.15	0.47	$5*10^{-6}$	$5*10^{-6}$	0.9999
	rs4886776	A	717	0.3	0.11	0.83	0.02	0.024	-
	rs893818	A	710	0.32	0.12	0.83	0.019	0.023	-
POAG									
Additive model	rs2165241	C	600	0.47	0.35	0.63	$3*10^{-7}$	$2*10^{-6}$	0.9999
	rs4886776	A	591	0.75	0.53	1.05	0.089	0.95	-
	rs893818	A	595	0.69	0.49	0.96	0.026	0.3	-
Dominant model	rs2165241	C	600	0.35	0.24	0.53	$3*10^{-7}$	$1*10^{-6}$	0.9999
	rs4886776	A	591	0.76	0.51	1.13	0.174	0.193	-
	rs893818	A	595	0.65	0.44	0.98	0.038	0.051	-
Recessive model	rs2165241	C	600	0.39	0.22	0.69	0.001	0.001	0.9248
	rs4886776	A	591	0.46	0.17	1.26	0.131	0.154	-
	rs893818	A	595	0.53	0.22	1.26	0.151	0.181	-

All results were obtained after adjustment for covariates, OR, odds ratio, 95%CI, 95% confidence interval.

TABLE 3. ASSOCIATIONS OF THE HAPLOTYPES RS2165241-RS4886776-RS893818 OF THE *LOXL1* GENE WITH XFG AND POAG.

Haplotype	Controls (n=396)	XFG patients (n=328)				POAG patients (n=208)			
		Frequency	OR	P	P_{perm}	Frequency	OR	P	P_{perm}
CAA	0.2163	0.1304	0.5	0.000099	0.001	0.1663	0.68	0.041	0.196
TAA	0.0245	0.0091	0.34	0.093	0.502	0.0181	0.64	0.436	0.982
CGA	0.0129	0.0118	1.92	0.321	0.942	0.009	2.11	0.891	1
CAG	0.0129	0.0138	1.04	0.572	0.999	0.0123	1.56	0.508	0.991
TAG	0.0143	0.0159	1.45	0.497	0.996	0.0152	1.84	0.308	0.916
CGG	0.2227	0.1073	0.45	8.4E-06	0.001	0.0996	0.35	1.4E-06	0.001
TGG	0.4963	0.6985	2.23	1.8E-09	0.001	0.6794	2.01	3E-07	0.001

The results were obtained by the logistic regression analysis with adjustment for covariates, OR, odds ratio, p, significance level.

of rs4886776, and G of rs893818 as increasing a risk for XFG/XFS and POAG, which contradicts to the results from Asian populations, in which these alleles were suggested to have a protective effect [7,8,13,20-24]. The observed allelic reversal may be explained by several factors related to the differences in the population genetic structure [26].

LOXL1 is a member of the lysyl oxidase family and is located on chromosome 15q22. The encoded protein is a copper-dependent amino oxidase catalyzing the first step of the cross-linking reaction between elastin and collagen [27]. The encoded protein is synthesized as a precursor and then is glycosylated and secreted out of the cells in the plasminogen state. *LOXL1* is converted to an active form by proteases and contributes to the formation of the extracellular matrix [28]. Therefore, its expression has been documented in ocular tissues, which might be involved in the formation of the extracellular matrix [25]. The effect of *LOXL1* gene polymorphisms (including rs2165241 analyzed in this study) on the expression of the extracellular matrix was demonstrated in several studies [7,12,21]. *LOXL1* overexpression can cause excessive collagen accumulation and result in XFG/XFS [29]. In the recent comprehensive bioinformatics analysis of the genes having been reported as candidates for POAG (termed "POAGome"), the *LOXL1* gene was mapped to the POAG-associated pathway "Extracellular matrix organization" [30].

The polymorphisms analyzed in the present study were located in the first intron of *LOXL1*. The genetic variants in this intron supposedly modify the activity of the *LOXL1-AS1* (Gene ID: 100287616, OMIM: 616800) promoter [31], influence RXRα transcription factor binding and affect the alternative splicing of *LOXL1* [21]. *LOXL1-AS1* (*LOXL1 antisense RNA 1*) is a long non-coding RNA [25]. It is ubiquitously expressed in XFS-affected tissues and its expression can be modified by XFS-relevant cell stressors that suggests

its key role in the cell stress response [31]. Inactivation of *LOXL1-AS1* altered the expression of up to 109 genes, 73 of which, including the extracellular matrix constituent gene, were downregulated, and 36 were upregulated [32]. The lncRNA *LOXL1-AS1* modulated expression of genes involved in the formation of collagen fibrils (*COL6A3*; Gene ID: 1293, OMIM: 120250), *LOXL4* (Gene ID: 84171, OMIM: 607318) and smooth muscles (*ACTA2*; Gene ID: 59, OMIM: 102620), extracellular matrix degradation (*TIMP3*; Gene ID: 7078, OMIM: 188826), calcium ion binding (*EFHD2*; Gene ID: 79180, OMIM: 616450), and reaction to oxidative stress (*HMOX1*; Gene ID: 3162, OMIM: 141250). All these genes play a role in XFG pathophysiology [32], and many of them (*TIMP3, ACTA2,* etc.) are candidates for POAG (collectively termed "POAGome") [30].

In summary, the present study provides evidence that the *LOXL1* gene polymorphisms (rs2165241, rs4886776, and rs893818) are associated with XFG and POAG in a Caucasian sample from central Russia. Along with the results of the other studies [7,9,13], this suggests the syntropic effects of the *LOXL1* gene in the development of XFG and POAG.

APPENDIX 1. THE LITERATURE DATA FROM GWAS ABOUT ASSOCIATIONS OF THE STUDIED POLYMORPHISMS *LOXL1* GENE WITH EXFOLIATION SYNDROME/GLAUCOMA.

To access the data, click or select the words "Appendix 1."

APPENDIX 2. THE REGULATORY POTENTIAL OF THE STUDIED SNPS.

To access the data, click or select the words "Appendix 2." (HaploReg, v4.1)
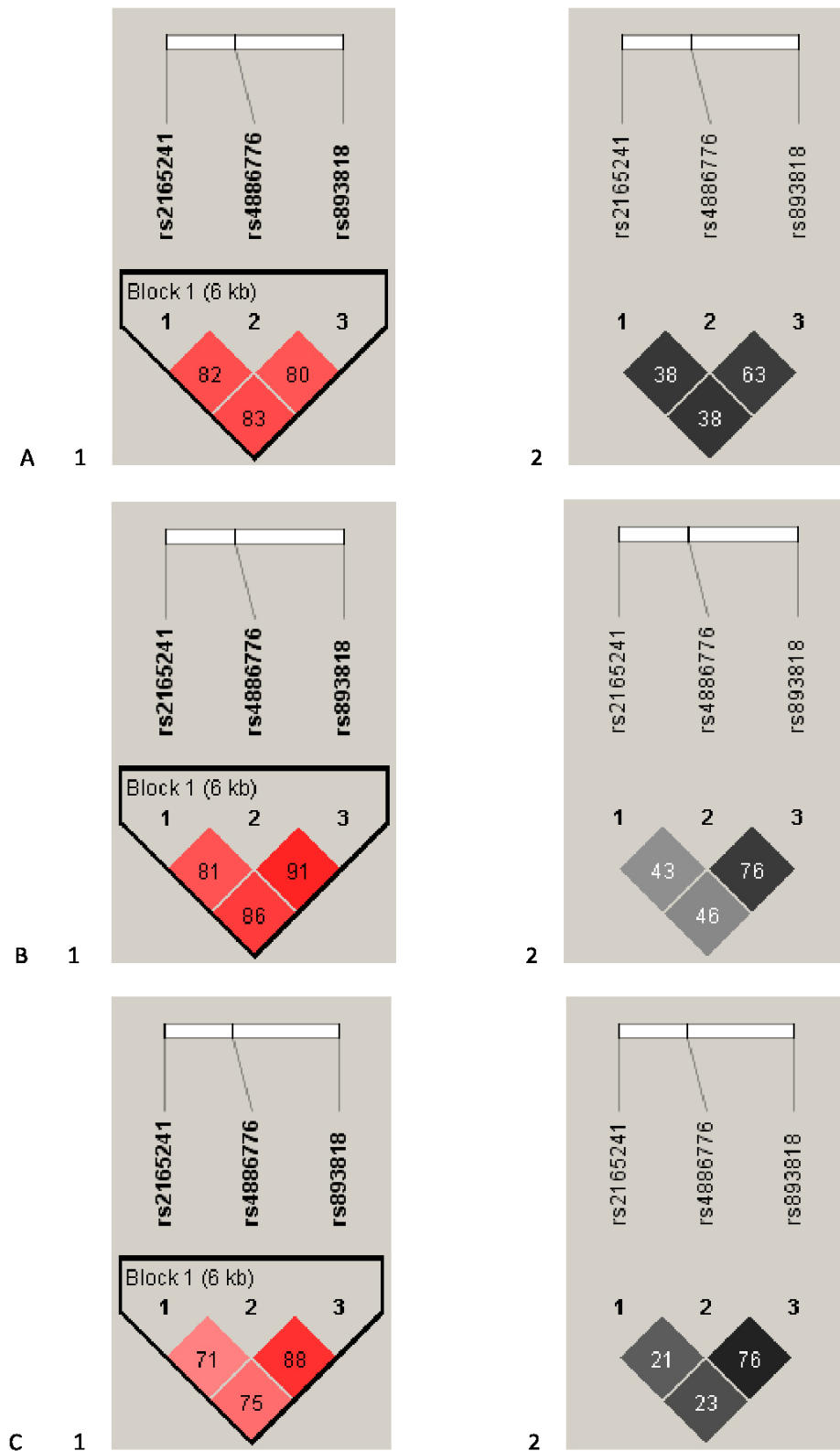
Figure 1. Linkage disequilibrium (LD) between SNPs rs2165241, rs4886776, rs893818 of the *LOXL1* gene in XFG (A), POAG (B) patients, and controls (C). LD values are presented as Lewontin's standardized coefficient D′ (left) and the square of the correlation Pearson's coefficient (r2; right) between SNPs.

APPENDIX 3. THE ALLELE AND GENOTYPE FREQUENCIES OF THE STUDIED *LOXL1* GENE SNPS IN THE CASE AND CONTROL GROUPS.

To access the data, click or select the words "Appendix 3."
Note: * minor allele homozygotes /heterozygotes/major allele homozygotes.

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