

Research Article

***RAD51B* (rs8017304 and rs2588809), *TRIB1* (rs6987702, rs4351379, and rs4351376), *COL8A1* (rs13095226), and *COL10A1* (rs1064583) Gene Variants with Predisposition to Age-Related Macular Degeneration**

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Received 14 August 2018; Accepted 27 March 2019; Published 2 May 2019

Academic Editor: Giuseppe Murdaca

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Background. Age-related macular degeneration (AMD) is a progressive neurodegenerative disease of a central part of the neural retina (macula) and a leading cause of blindness in elderly people. While it is known that the AMD is a multifactorial disease, genetic factors involved in lipid metabolism, inflammation, and neovascularization are currently being widely studied in genome-wide association studies (GWAS). The aim of our study was to evaluate the impact of new single nucleotide polymorphisms (SNPs) in *RAD51B*, *TRIB1*, *COL8A1*, and *COL10A1* genes on AMD development. **Methods.** Case-control study involved 254 patients diagnosed with early AMD, 244 patients with exudative AMD, and 942 control subjects. The genotyping of *RAD51B* (rs8017304 and rs2588809), *TRIB1* (rs6987702, rs4351379, and rs4351376), *COL8A1* (rs13095226), and *COL10A1* (rs1064583) was carried out using TaqMan assays by a real-time polymerase chain reaction (RT-PCR) method. **Results.** Statistically significant difference was found in genotype (TT, TC, and CC) distribution of *COL8A1* rs13095226 between exudative AMD and control groups (60.2%, 33.6%, and 6.1% vs. 64.9%, 32.3%, and 2.9%, respectively, $p = 0.036$). Also, comparing with TT+TC, rs13095226 CC genotype was associated with 3.5-fold increased odds of exudative AMD development (OR = 3.540; 95% CI: 1.415-8.856; $p = 0.007$). **Conclusion.** Our study revealed a strong association between a variant in *COL8A1* (rs13095226) and exudative AMD development.

1. Introduction

Age-related macular degeneration (AMD) is a progressive neurodegenerative disease of a central part of neural retina (macula) [1]. AMD is a leading cause of central vision loss, and while it is diagnosed in elderly people (in those aged 60 and over) [1], the first signs of the disease can occur in people aged 40 [2]. One of the main processes involved in AMD pathogenesis is called drusenogenesis [3]. Drusen are described as small particles of lipid, protein, and collagen detachments

accumulated between the retinal pigment epithelium (RPE) and the Bruch's membrane (BrM) in the retina [3]. RPE controls fluid transportation between the choriocapillaris and the retina including lipid transportation and metabolism as well as oxygen transportation [4]. The BrM is a five-layer extracellular matrix located between the RPE and the choroid. It regulates metabolic exchange between RPE cells and blood flow from the choroid through a semipermeable filtration barrier [5]. Any alteration in the structure of BrM might impact dysfunction of the RPE and the outer retina [6]. One

of the most complicated biological processes which may affect BrM is ageing: age-related processes urge the accumulation of incompletely digested phospholipids [7], combining with oxidative stress results of lipid peroxidation [8] and lysosomal defects in photoreceptor outer segments [9]. Oxidative stress-induced lipid and protein accumulation leads to RPE injury or early RPE cell death with changes in BrM [10, 11]. Damaged RPE cells release huge amounts of different cytokines and chemokines which could result in chronic inflammation over time [12–14]. One of the cytokines is a vascular endothelial growth factor A (VEGF-A) which can also induce angiogenesis [15–17]. This process leads to a growth of new fragile and leaky vessels resulting in exudative hemorrhage and acute vision loss [18]. According to the Age-Related Eye Disease Study (AREDS), AMD can be classified into early, intermediate, and late stages [19]. Early AMD is described as the appearance of drusen and retinal pigment abnormalities; when at least one large druse, numerous medium-sized drusen, or geographic atrophy (GA) without extension to the center of the macula occurs, the intermediate stage of AMD is diagnosed; late AMD is divided into dry AMD with the GA of the RPE and neovascular AMD which is characterized by choroidal neovascularization with detachments of the RPE, hemorrhages, and/or scars [20]. While it is known that the AMD is a multifactorial disease, genetic factors involved in lipid metabolism, inflammation, and neovascularization are currently being widely studied in genome-wide association studies (GWAS). Products of a collagen gene family are composed of types I, II, III, and V of fibril-forming interstitial and type IV basement membrane collagens. Collagens keep the architecture and function of normal tissues as well as the structure and function of the extracellular matrix [21, 22]. Recent studies detected an intronic variant in *COL8A1* gene (rs13095226 T/C), suggesting an association with advanced AMD [23–27]. The *COL8A1* gene is located on human chromosome 3 and encodes one of the two alpha chains of type VIII collagen which is a central component of multiple basement membranes of corneal endothelial cells, including BrM, choroidal stroma, and endothelia of blood vessels, playing a role in the maintenance of vascular integrity and structure [28, 29]. BrM and new vessel formation play a key role in pathogenesis of AMD [30]. Another collagen gene family member is *COL10A1* gene, located on human chromosome 6, which encodes the alpha chain of type X collagen. This short-chain collagen is expressed by hypertrophic chondrocytes during endochondral ossification, and it was shown that the expression of *COL10A1* was significantly downregulated in patients with osteoarthritis [31], but its expression was higher in diverse solid tumors and correlated with tumor vasculature [32]. The new variant near *FRK/COL10A1* (rs1999930) was found to be associated with advanced AMD development [24] and suggested the *COL10A1* as a potential locus for future association studies. While the oxidative stress has been linked to the various types of DNA damage playing a significant role in ageing and age-related disorders [33, 34], few studies [35, 36] revealed a significant association between oxidative stress-linked DNA damage and AMD development. Recently, GWAS pinpointed new genetic variations

in the *RAD51B* gene associated with AMD [25, 26, 37, 38]. *RAD51B* is involved in homologous recombinational repair of DNA double-strand breaks by promoting the activity of the central recombinase [39]. Absence of *RAD51B* protein is thought to disrupt the formation of the *RAD51* nucleoprotein filament, which is the initial stage of homologous recombinational repair [40]. G-protein-coupled receptor-induced proteins, playing a role in the mitogen-activated protein kinases- (MAPK-) related signaling cascade [41, 42] which mediates cell proliferation, differentiation, and apoptosis [43] and can regulate lipid metabolism through this pathway [44], are encoded by tribbles pseudokinase 1 (*TRIB1*) gene located in human chromosome 8. It has also been suggested that the *TRIB1* expression is regulated by inflammatory stimulation [45]. There was found one SNP in *TRIB1* gene (rs6987702) to be associated with AMD in African American and Mexican American population [46], suggesting a significant role of *TRIB1* in AMD development.

Association studies of these SNPs, however, have not been conducted in both (early and exudative) AMD forms. Genetic differences between developments of early and exudative AMD still need to be researched and understood better which might lead to future studies with focus on certain molecular pathways involved in the pathogenesis of AMD. Also, genetic variations combined with other risk factors or molecular changes can benefit physicians in creating personalized genetic therapies and/or lifestyle programs for increased risk individuals.

Considering previously studied links between genetic variations and AMD, we chose three previously described SNPs in *RAD51B* (rs8017304), *TRIB1* (rs6987702), and *COL8A1* (rs13095226) and four new genetic loci in *RAD51B* (rs2588809), *TRIB1* (rs4351376 and rs4351379), and *COL10A1* (rs1064583) genes as potential biomarkers for early and exudative AMD. The aim of our study was to determine and evaluate their impact on the development of early and exudative AMD in the Lithuanian population.

2. Materials and Methods

The study was conducted in the Department of Ophthalmology, Hospital of Lithuanian University of Health Sciences and Laboratory of Ophthalmology, Neuroscience Institute, Lithuanian University of Health Sciences. Ethical approval was obtained from the Ethics Committee for Biomedical Research (number: BE-2-/13).

Ophthalmological evaluation, study group formation, DNA extraction and genotyping methods, and statistical analysis were described in detail in our previous studies [47, 48].

3. Results

3.1. Demographic Characteristics of the Study Groups. Our study involved 498 patients (254 patients with a diagnosis of early AMD and 244 patients with exudative AMD) and 942 healthy controls. The control group was formed of 942 subjects classified into different genders, which matched gender classification in the early and exudative AMD group

TABLE 1: Demographic characteristics.

Characteristic	Group			<i>p</i> value
	Early AMD (<i>n</i> = 254)	Exudative AMD (<i>n</i> = 244)	Control (<i>n</i> = 942)	
Gender				
Male, <i>n</i> (%)	83 (32.7)	87 (35.7)	350 (37.2)	0.188*
Female, <i>n</i> (%)	171 (67.3)	157 (64.3)	592 (62.8)	0.665**
Age (years), median (IQR)	73 (12)	76 (11)	53 (0)	<0.001* <0.001**

*Early AMD group vs. the control group. **Exudative AMD group vs. the control group.

TABLE 2: Analysis of Hardy-Weinberg equilibrium in control group subjects.

SNP	Allele frequencies		Genotype distribution in the control group	<i>p</i> value
	G	A		
<i>RAD51B</i> rs8017304	G (0.31)	A (0.69)	90/401/451	0.950
<i>RAD51B</i> rs2588809	T (0.12)	C (0.88)	17/185/740	0.175
<i>TRIB1</i> rs6987702	C (0.27)	T (0.73)	83/343/516	0.019
<i>TRIB1</i> rs4351379	C (0.07)	G (0.94)	7/109/826	0.111
<i>COL8A1</i> rs13095226	C (0.19)	T (0.81)	27/304/611	0.138
<i>COL10A1</i> rs1064583	G (0.31)	A (0.69)	52/482/408	<0.001

structure; however, subjects of the control group were younger than AMD patients ($p < 0.001$) (Table 1).

3.2. Hardy-Weinberg Equilibrium. When genotyping results showed that G allele at *TRIB1* rs4351376 was observed in all study subjects (100%), it was not included in further analysis. Hardy-Weinberg equilibrium (HWE) analysis showed that the distribution of genotypes of rs6987702 and rs1064583 deviated from the HWE in the control group and those two SNPs were excluded from further statistical analysis as well (Table 2).

3.3. Analysis of Single Nucleotide Polymorphisms. Analysis of four SNPs (rs8017304, rs2588809, rs4351379, and rs13095226) in the early and exudative AMD and control groups showed a statistically significant difference only in genotype (TT, TC, and CC) distribution of *COL8A1* rs13095226, when compared to the exudative AMD and control groups (60.2%, 33.6%, and 6.1% vs. 64.9%, 32.3%, and 2.9%, respectively, $p = 0.036$) (Table 3).

Binomial logistic regression revealed that the rs13095226 CC genotype is associated with 3.5-fold increased odds of exudative AMD development under the recessive model (OR = 3.540; 95% CI: 1.415-8.856, $p = 0.007$) as well as under the codominant model (OR = 3.426; 95% CI: 1.355-8.667, $p = 0.009$) (Table 4). Results remained statistically significant even after applying Bonferroni correction ($p < 0.05/4$) (Table 4).

3.4. Haplotype Associations with AMD. In this section, we performed haplotype association analysis and evaluated the impact of haplotype constructed of two SNPs: rs8017304

and rs2588809 on early and exudative AMD development. Linkage disequilibrium (LD) analysis was assessed by both D' and r^2 measures. The r^2 values were 0.055 and 0.063 in early AMD and exudative AMD analysis, respectively; for the haplotype block, $|D'|$ values were 0.425 and 0.457 in early AMD and exudative AMD analysis, respectively.

Unfortunately, haplotype analysis did not reveal any significant associations with early or exudative AMD development after adjustment for age.

4. Discussion

Our study involved 498 AMD patients (254 patients with the diagnosis of early AMD and 244 patients with exudative AMD) and 942 healthy control subjects. Since we chose 7 SNPs, 5 of those were newly selected as risk factors for AMD development, *RAD51B* (rs2588809), *TRIB1* (rs6987702, rs4351376, and rs4351379), and *COL10A1* (rs1064583), and 2 were already associated with AMD development, *RAD51B* (rs8017304) and *COL8A1* (rs13095226). Unfortunately, our study revealed only one SNP (rs13095226) which was associated with 3.5-fold increased odds for exudative AMD development in the population of Lithuania ($p = 0.007$).

One of the SNPs near the *TRIB1* locus called rs17321515 was found affecting lipoprotein metabolism. It was strongly associated with triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) and even with increased risk of coronary heart disease (CHD), but results remain controversial among the studies [49–51]. Another SNP (rs2954021) located in *TRIB1* gene was associated with increasing plasma TG levels and coronary artery disease (CAD) risk [52, 53] as well as the other three variants: rs2001945, rs2001845, and rs2001844 [54]. Furthermore, rs2001844 was associated with increased plasma TG and reduced HDL-C [54]. Several association studies reported a significant association between HDL-C and AMD development as well [55–59]; unfortunately, others did not reveal any significant associations between HDL-C and AMD development [60–66]. On the other hand, while the association of HDL-C and AMD is controversial, variant in lipid trait-associated gene *TRIB1* rs6987702 showed a significant association with AMD development, but those results did not survive strict corrections for multiple testing [46]. In our study, none of the SNPs in *TRIB1* reached a statistically significant association with early or exudative AMD development.

TABLE 3: *RAD51B* (rs8017304 and rs2588809), *TRIB1* (rs4351379), and *COL8A1* (rs13095226) SNPs in patients with early and exudative AMD and control groups.

Gene/marker	Genotype/allele	Early AMD, n (%)	Control group, n (%)	<i>p</i> value	Exudative AMD, n (%)	Control group, n (%)	<i>p</i> value
<i>RAD51B</i> rs8017304	AA	125 (49.2)	451 (47.9)	0.745	117 (48.0)	451 (47.9)	0.423
	AG	102 (40.2)	401 (42.6)		110 (45.1)	401 (42.6)	
	GG	27 (10.6)	90 (9.6)	17 (7.0)	90 (9.6)		
	A	352 (69.3)	1303 (69.2)	0.955	544 (70.5)	1303 (69.2)	
	G	156 (30.7)	581 (30.8)	144 (29.5)	581 (30.8)	0.570	
<i>RAD51B</i> rs2588809	CC	196 (77.2)	740 (78.6)	0.410	188 (77.0)	740 (78.6)	0.652
	CT	50 (19.7)	185 (19.6)		53 (21.7)	185 (19.6)	
	TT	8 (3.1)	17 (1.8)	3 (1.2)	17 (1.8)		
	C	442 (87.0)	1665 (88.4)	0.398	429 (87.9)	1665 (88.4)	
	T	66 (13.0)	219 (11.6)	59 (12.1)	219 (11.6)	0.775	
<i>TRIB1</i> rs4351379	GG	214 (84.3)	826 (87.7)	0.229	217 (88.9)	826 (87.7)	0.780
	GC	39 (15.4)	109 (11.6)		26 (10.7)	109 (11.6)	
	CC	1 (0.4)	7 (0.7)	1 (0.4)	7 (0.7)		
	G	467 (91.9)	1761 (93.5)	0.222	460 (94.3)	1761 (93.5)	
	C	41 (8.1)	123 (6.5)	28 (5.7)	123 (6.5)	0.524	
<i>COL8A1</i> rs13095226	TT	166 (65.4)	611 (64.9)	0.095	147 (60.2)	611 (64.9)	0.036
	TC	74 (29.1)	304 (32.3)		82 (33.6)	304 (32.3)	
	CC	14 (5.5)	27 (2.9)	15 (6.1)	27 (2.9)		
	T	406 (79.9)	1526 (81.0)	0.585	376 (77.0)	1526 (81.0)	
	C	102 (20.1)	358 (19.0)	112 (23.0)	358 (19.0)	0.051	

AMD: age-related macular degeneration. *p* value < 0.05 indicated in bold is statistically significant.

TABLE 4: Binomial logistic regression analysis of the *COL8A1* (rs13095226) in patients with exudative AMD and controls.

SNP	Exudative AMD		AIC value
	Model/genotype	OR; 95% CI; <i>p</i> *	
rs13095226	<i>Codominant</i>		640.511
	TC vs. TT	0.906; 0.589-1.394; 0.653	
	CC vs. TT	3.426; 1.355-8.667; 0.009	
rs13095226	<i>Recessive</i>		638.713
	CC vs. TT+TC	3.540; 1.415-8.856; 0.007	

**p* was adjusted for age in logistic regression models. OR: odds ratio; 95% CI: 95% confidence interval; AIC: akaike information criterion.

Studies of variants in *RAD51B* revealed statistically significant associations of SNPs in *RAD51B* with breast cancer occurrence [67–70]. Also, *RAD51B* rs911263 was associated with rheumatoid arthritis (RA) [71, 72]; two SNPs (rs11158728 and rs927220) were associated with nasopharyngeal carcinoma development [73], and one (rs34094401) was associated with Parkinson’s disease [74]. Also, literature review explains that risk alleles at *RAD51B* rs8017304, rs13081855 near *COL8A1/FILIP1L* locus, and rs3812111 in *COL10A1* are associated with a greater risk for advanced AMD development [25]. Other three GWAS proved *RAD51B* gene association with AMD as well [26, 37, 38]. Seddon et al. conducted a 12-year follow-up study of 2765 individuals and revealed that *RAD51B* (HR: 0.8; 95% CI: 0.60-0.97, *p* = 0.03) was significantly related to AMD progression [26]. In another study, Seddon and coauthors [38] analyzed the

progression of AMD and found 834 from 2951 subjects, who progressed from no AMD, early AMD, or intermediate AMD to an advanced AMD form, and also confirmed that *RAD51B* was associated with AMD progression. Fritsche et al. [25] also proved a strong *RAD51B* association (*p* < 5×10^{-8}) with advanced AMD in Europeans and Asians. Chu et al. analyzed *RAD51B* influence on AMD using two cohorts from Caucasian and Han Chinese populations, as well. Scientists identified two new SNPs in *RAD51B* (rs17105278 and rs4902566) and confirmed the association between rs8017304 and AMD development in Caucasians [37], suggesting a significant role of *RAD51B* associated with DNA damage/DNA repair mechanism in AMD pathogenesis.

Recent studies indicated that variants in *COL8A1* gene were associated with AMD development [24–26, 38]. One of the GWAS studies was performed on 979 patients with advanced AMD and 1709 control subjects and revealed a significant association between rs13095226 and AMD (*p* = $2.5e - 06$) in the European population [23]. Also, in this study, authors found that the frequencies of minor allele C at rs13095226 in patients with polypoidal choroidal vasculopathy (PCV), neovascular AMD (nAMD), and controls were similar to the frequencies in Americans, while differences were found between Americans and Asians [23]. Meta-analysis of advanced AMD confirmed previously found associations to advanced AMD [24], while in contrast, Yang et al.’s study including 300 cases with nAMD, 300 cases with PCV, and 300 control subjects did not show the association of *COL8A1* rs13095226 with nAMD or PCV, suggesting that

this variant may not be a risk factor for nAMD or PCV in Chinese subjects [75]. Also, another variant of the same gene, polymorphism of *COL8A1* rs13081855, was linked to exudative AMD development [27]. As in non-AMD patients, one of the common variants in *COL8A1* gene (rs669676) was found to be associated with myopic choroidal neovascularization (OR: 1.88; 95% CI: 1.18-2.98, $p = 0.0076$) but did not survive multiple testing [74]. Our study of the Lithuanian population discovered a strong association between a variant in *COL8A1* (rs13095226) and exudative AMD development; genotype rs13095226 CC was determined to be associated with 3.5-fold increased odds of exudative AMD development.

We also found a study, which showed the contribution of the extracellular collagen matrix (FRK/*COL10A1*) pathways to the development of advanced AMD. A coding variant rs3812111 in *COL10A1*, a collagen protein, could be involved in maintaining the structure and function of the extracellular matrix [24]. Ferrington et al. analyzed that the *COL10A1* rs3812111 A/T (nonrisk allele/risk allele) ratio was 0.69/0.65 in controls/age-related macular degeneration [76]. To our knowledge, there are no studies analyzing *COL10A1* (rs1064583) polymorphism in patients with AMD.

The following limitations of this study have to be declared:

- (i) Patients with atrophic AMD have not been analyzed
- (ii) Sample size of AMD and healthy controls was relatively small
- (iii) Possibility of other risk factors was not included in the study

A thorough medical examination of the study objects can be acknowledged as one of the main strengths of our study. All patients were examined for chronic infectious and noninfectious diseases by a general practitioner. It is also important to highlight that RAD51B (rs8017304 and rs2588809), TRIB1 (rs6987702, rs4351379, and rs4351376), *COL8A1* (rs13095226), and *COL10A1* (rs1064583) gene variants have never been studied in the Baltic states, namely, in the Lithuanian population, and our study was the first of its type.

5. Conclusion

Our study revealed a strong association between variant in *COL8A1* (rs13095226) and exudative AMD development.

Data Availability

The genotyping data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

None of the authors have any proprietary interests or conflicts of interest related to this submission.

Acknowledgments

This work was funded by a grant (No. SEN-11/2015) from the Research Council of Lithuania.

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