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Associations between *CYP2C8* rs10509681 and rs11572080 gene polymorphisms and age-related macular degeneration

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Background. Age-related macular degeneration (AMD) is the most common cause of irreversible visual loss in industrialized countries. Early symptoms of AMD include drusen and changes in retinal pigment epithelium. However, the etiology of AMD and drusen formation is not fully understood. Recent studies suggest that *CYP2C8*-related metabolic processes might play an important role in the development of AMD. The aim of our study is to investigate *CYP2C8* rs10509681 and *CYP2C8* rs11572080 genotype frequencies in patients with early AMD and to compare them with healthy controls.

Materials and Methods. The study enrolled 305 patients with early AMD and 300 healthy controls. The genotyping of *CYP2C8* rs10509681 and *CYP2C8* rs11572080 was carried out using the real-time PCR method.

Results. The analysis of studied *CYP2C8* polymorphisms did not reveal any statistically significant differences between the AMD and the control groups. For the *CYP2C8* rs10509681 gene polymorphism the distribution of T/T, T/C, and C/C genotypes was 83.3%, 16.7%, and 0% vs. 83.7%, 15.7%, and 0.7%, $p = 0.343$. For the *CYP2C8* rs11572080 gene polymorphism the distribution of C/C, T/C and T/T and genotypes was 84.9%, 15.1%, and 0% vs. 82.3%, 17.3%, and 0.3%, $p = 0.447$.

Conclusion. The study revealed that there were no statistically significant differences in the distribution of *CYP2C8* rs10509681 and *CYP2C8* rs11572080 genotypes in patients with early AMD and in healthy controls.

Keywords: Age-related macular degeneration, cytochrome P450, rs10509681, rs11572080, gene polymorphisms

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INTRODUCTION

Age-related macular degeneration (AMD) is a degenerative disease that affects the central part of the retina. Specific changes in the macular area such as drusen formation and changes in retinal pigment epithelium (RPE) in the absence of the other ophthalmological pathologies characterize AMD (1). It is the most common cause of blindness in the developed countries (1) and usually affects persons older than 50 years of age (2).

In addition to age, AMD has been reported to have multiple risk factors including gender, race, obesity, hypercholesterolemia, hyperglycaemia, heart diseases, hypertension, iris colour, hyperopia, lifestyle (smoking, alcohol abuse, eating disorders, physical inactivity, stress), and environmental factors such as ultraviolet radiation (3–6). For example, it was found that the more cigarettes were smoked per day, the greater was the likelihood of developing AMD, and vice versa – quitting smoking reduced the risk (2, 7, 8). Individuals who did not smoke for more than 20 years had the same probability of developing AMD as people who had never smoked (2). Also, the risk of AMD development is increased by a diet low in antioxidants, namely, vitamins C and E, carotenoids (lutein and zeaxanthin), and zinc. Healthier food or dietary supplements correlate with a slower progression of AMD (2). The best food for AMD prevention contains omega-3 polyunsaturated fatty acids, which are mostly found in oily fish (salmon, herring). In contrast, food containing saturated fats increases the risk of AMD (2).

Composed mostly of lipids, the extracellular deposits or drusen are the hallmark of AMD (9). These deposits build up beneath RPE and Bruch's membrane (1) resulting in damage and redistribution of RPE cells (10). Disruption of the oxygen metabolism leads to photoreceptor degeneration associated with the impairment of visual functions (11).

Drusen develop during immune-mediated metabolic processes. Genetic factors related to lipid metabolism are thought to play a role in the progression of the AMD. However, the exact mechanism by which the lipids accumulate in RPE is not fully understood. Some authors speculate that the origin of the lipids in the drusen is the circulatory system associated with cholesterol changes in the blood (11); others speculate that the deposits are a consequence of the locally produced lipoproteins of the Bruch's membrane with different density and structure (12). The latter hypothesis is supported by the observation that an oxidative stress leads to the impairment of barrier properties and increased permeability of Bruch's membrane (13). It is believed that genetic factors may have a significant impact on the development of the disease. One of the candidates is the Cytochrome P450 2C8 (*CYP2C8*) gene, a member of the multifunctional oxidase system, involved in the metabolism of xenobiotics. It is also responsible for the activity of the epoxygenases involved in the metabolism of the long chain polyunsaturated fatty acids, such as eicosapentaenoic acid and docosapentaenoic acid – the omega 3 fatty acids found in fish oil (14, 15). As unsaturated fatty acids have a beneficial impact on AMD, the polymorphisms of the *CYP2C8* gene may be involved in the development of AMD.

In addition, a comparison of AMD and Alzheimer's disease (reviewed in Çerman et al.) indicates common pathological pathways. Both AMD and Alzheimer's disease share common features such as vitronectin and amyloid-β accumulation, increased oxidative stress, apolipoprotein and complement activation pathways (16). A study by Yan et al. identified *CYP2J2* rs890293 being a possible predisposing genetic factor for late-onset Alzheimer's disease progression in the Chinese Han population (17). These findings have led us to the hypothesis that the genes involved in the pathogenesis of Alzheimer's disease and lipid metabolism, such as genes of the cytochrome P450 family, may be associated with AMD. Therefore, *CYP2C8* rs10509681 and *CYP2C8* rs11572080 single nucleotide polymorphisms were chosen to be investigated in patients with early AMD.

Here we report the frequencies of *CYP2C8* rs10509681 and *CYP2C8* rs11572080 genotypes in patients with early AMD in the Lithuanian population.

MATERIALS AND METHODS

Ethics statement

Permission to conduct the study was obtained from the Ethics Committee for Biomedical Research (No. BE-2-/13). All donors provided written

informed consent in accordance with the Declaration of Helsinki.

Study population

A total of 305 patients with the diagnosis of early AMD were enrolled in the study, based on exclusion criteria described below. The control group comprised 300 persons who had no ophthalmologic pathology on examination and agreed to participate in the study. The AMD patients and the controls were matched by age and gender ($p > 0.05$) (Table 1).

Table 1. Demographic characteristics of the study population

Characteristic	Group		*p* value
	AMD *n* = 305	Control *n* = 300	
Men, *n* (%)	91 (29.84)	77 (25.67)	0.252*
Women, *n* (%)	214 (70.16)	223 (74.33)	
Age, mean	67.52	66.42	0.9994*

* not significant – $p > 0.05$

For the analysis, the study population was divided into two groups according to their age: younger than 65 years; and 65 years and older.

Ophthalmological evaluation

Ophthalmological evaluation for all subjects in our study was carried out as described above (18).

DNA extraction and genotyping

DNA was extracted from leucocytes using a GeneJET Genomic DNA Purification Kit (Thermo Scientific). The polymorphisms (rs10509681 and rs11572080) in the *CYP2C8* gene were analyzed using TaqMan® Drug Metabolism assays (Applied Biosystems, USA) on a Rotor-Gene Q RT-PCR system (Qiagen, USA). DNA extraction and genotyping were performed following the same procedure described earlier (18).

Statistical analysis

Statistical analysis was performed using SPSS/W 20.0 software (Statistical Package for the Social Sciences for Windows, Inc., Chicago, Illinois, USA). The data are presented as absolute numbers with percentages and mean values. The frequencies of genotypes (in percentage) are presented in Table 2.

Table 2. Frequency of *CYP2C8* rs10509681 and *CYP2C8* rs11572080 genotypes in all patients with early AMD and in control group

Gene marker	Genotype/Allele	Control n (%) (*n* = 300)	*p* value HWE	AMD n (%) (*n* = 305)	*p* value HWE	*p* value
CYP2C8	GenotypeT/T					
rs10509681						
	T/C	251 (83.7)	0.901	254 (83.3)	0.112	0.343
	C/C	47 (15.7)		51 (16.7)		
	Total	2 (0.7)		0 (0)		
	Allele	300 (100)		305 (100)		
	T	495 (83.62)		264 (88)		
	C	97 (16.38)		36 (12)		
CYP2C8	Genotype					
rs11572080						
	C/C	247 (82.3)	0.313	259 (84.9)	0.154	0.447
	C/T	52 (17.3)		46 (15.1)		
	T/T	1 (0.3)		0 (0)		
	Total	300 (100)		305 (100)		
	Allele					
	C	546 (91)		564 (92.46)		
	T	54 (9)		46 (7.54)		

Hardy-Weinberg analysis was performed to compare the observed and expected frequencies of *CYP2C8* rs10509681 and *CYP2C8* rs11572080 using the χ^2 test in all groups. The distribution of both (rs10509681 and rs11572080) SNPs in AMD and control groups were compared using the χ^2 test or the Fisher exact test. Binomial logistic regression analysis was performed to estimate the impact of genotypes on the development of AMD. Odds ratios and 95% confidence intervals were calculated but did not show any statistical significance. Differences were considered statistically significant when $p < 0.05$.

RESULTS

The frequencies of *CYP2C8* rs10509681 and *CYP2C8* rs11572080 genotypes in all healthy controls and patients with early AMD are shown in Table 2. The distribution of *CYP2C8* rs10509681 and *CYP2C8* rs11572080 genotypes and alleles in all patients with early AMD and in the control group was consistent with the Hardy-Weinberg equilibrium. The analysis of *CYP2C8* rs10509681 and *CYP2C8* rs11572080 gene polymorphisms including all subjects did not reveal any differences in the distribution of genotypes and between the patients with AMD and the controls (*CYP2C8* rs10509681 gene polymorphism genotypes T/T, T/C, and C/C (83.3%, 16.7%, and 0% vs. 83.7%, 15.7%, and 0.7%, $p = 0.343$); and *CYP2C8* rs11572080 gene polymorphism genotypes C/C, T/C and T/T (84.9%, 15.1%, and 0% vs. 82.3%, 17.3%, and 0.3%, $p = 0.447$).

The comparison of the frequency of *CYP2C8* rs10509681 and *CYP2C8* rs11572080 genotypes in age groups did not show any significant differences (Table 3).

The comparison of the frequency of *CYP2C8* rs10509681 and *CYP2C8* rs11572080 genotypes by gender did not show any significant differences either (Table 4).

Binomial logistic regression analysis in the patients with AMD and in the control group did not reveal any significant variables either.

Table 3. Frequency of *CYP2C8* rs10509681 and *CYP2C8* rs11572080 genotypes in patients with early AMD and control subjects by age

Gene	Genotype/ Allele	<65 years		*p* value	≥65 years		*p* value
		AMD *n* (%)	Control *n* (%)		AMD *n* (%)	Control *n* (%)	
CYP2C8	Genotype						
rs10509681							
	T/T	78 (87.6)	184 (83.6)	0.510	176 (81.5)	67 (83.3)	0.734
	T/C	11 (12.4)	34 (15.5)		40 (18.5)	13 (16.2)	
	C/C	0 (0)	2 (0.9)		0 (0)	0 (0)	
	Allele						
	T	167 (93.82)	402 (31.36)		184 (87.71)	147 (91.875)	
	C	11 (6.18)	38 (8.64)		29 (12.29)	13 (8.125)	
CYP2C8	Genotype						
rs11572080	C/C	80 (89.9)	183 (82.8)	0.160	179 (82.9)	64 (81.0)	0.250
	C/T	9 (10.1)	38 (17.2)		37 (17.1)	14 (17.7)	
	T/T	0 (0)	0 (0)		0 (0)	1 (1.3)	
	Allele						
	C	169 (94.94)	404 (91.4)		395 (91.44)	142 (89.87)	
	T	9 (5.06)	38 (8.6)		37 (8.56)	16 (10.13)	

Table 4. Frequency of *CYP2C8* rs10509681 and *CYP2C8* rs11572080 genotypes in patients with early AMD and control group by gender

Gene	Genotype/ Allele	Men		*p* value	Women		*p* value
		AMD *n* (%)	Control *n* (%)		AMD *n* (%)	Control *n* (%)	
CYP2C8	Genotype						
rs10509681							
	T/T	81 (89.0)	64 (83.1)	0.368	173 (80.8)	187 (83.9)	0.452
	T/C	10 (11.0)	12 (15.6)	0.492	41 (19.2)	35 (15.7)	0.378
	C/C	0 (0)	1 (1.3)	0.458	0 (0)	1 (0.4)	1.00
	Allele						
	T	172 (94.51)	140 (90.91)		106 (49.07)	409 (91.7)	
	C	10 (5.)	12 (9.09)		110 (50.93)	37 (8.3)	
CYP2C8	Genotype						
rs11572080							
	C/C	82 (90.1)	63 (81.8)	0.176	177 (82.7)	184 (82.5)	1.00
	C/T	9 (9.9)	13 (16.9)	0.251	37 (17.3)	39 (17.5)	1.00
	T/T	0 (0)	1 (1.3)	0.458	0 (0)	0 (0)	1.00
	Allele						
	C	173 (95.05)	139 (90.26)		391 (91.36)	407 (91.26)	
	T	9 (4.95)	14 (9.74)		37 (8.64)	39 (8.74)	

DISCUSSION

We observed no statistically significant differences between the AMD group (n = 305) and the control group (n = 300) in the distribution of *CYP2C8* gene rs10509681, rs11572080 polymorphism genotypes. Neither did we find any statistically significant differences in polymorphisms according to the age or gender. To the best of our knowledge, we are the first to investigate the *CYP2C8* gene polymorphisms in AMD patients. On the basis of our research results, we conclude that *CYP2C8* gene rs10509681 and rs11572080 polymorphisms are not associated with the manifestation of early AMD.

Similar to our results, no differences between disease and control groups for the *CYP2C8* were reported in colorectal cancer and coronary heart disease. Ladero et al. investigated *CYP2C8* gene polymorphism rs11572080 in patients with colorectal cancer (n = 153) and in healthy individuals (n = 298) (19). In this study, *CYP2C8* rs11572080 genotype distribution in healthy Spanish subjects were: T/T 67.8%, T/C 30.2%, C/C 2.0% (19), while the genotype distribution in our group of healthy subjects was: the T/T genotype was dominant and was observed in 82.3% of patients, the T/C genotype in 17.3% of patients, and the C/C in 0.3%. Craig et al investigated *CYP2C8* rs10509681 gene polymorphism in 980 patients with coronary heart disease and 1085 healthy individuals (20). The C/C genotype was observed in 81.3% of patients, while the results of C/T and T/T genotypes were summed up and made up 18.7%, which is similar to our findings (CC 83.7%, C/T 15.7%, TT 0.7% – Table 2) (20). Our reported *CYP2C8* gene polymorphism distribution in healthy Lithuanian population is consistent with previous reports.

CYP2C8 gene polymorphisms were found to be associated with essential hypertension (EH) (21). *CYP2C8**3 allele was statistically significantly more frequent in men with EH (21). Arterial hypertension (AH) is one of the risk factors that would provoke AMD, regardless of gender (22). AH can damage

arteries and arteriolars of the rear submacular area, causing local ischemia and impeding the removal of metabolic products, which leads to AMD development (23). In 2003, Klein et al. suggested that the risk of the development of exudative AMD increases 1.5-fold in men with hypertension (24). Therefore, we assumed that *CYP2C8* (rs10509681 and rs11572080) polymorphisms may be associated with the development of exudative AMD in men, especially in patients with arterial hypertension. However, our results do not corroborate such assumptions.

CYP2C8 gene (rs10509681 and rs11572080) polymorphism has been reported to be associated with drug metabolism (reviewed in Daily E et al.). For example, the association between the *CYP2C8* gene and serum lipid-lowering drugs was noticed, particularly with cerivastatin and, to a lesser extent, with fluvastatin and simvastatin (25). In the review, a close relationship was concluded not only between *CYP2C8* and AMD risk factors such as hyperglycaemia, hypercholesterolemia, obesity, hypertension, and heart disease, but also between the medications that control risk factors and metabolism.

The main limitations of this study are that it did not investigate the patients with late forms of AMD (exudative and atrophic). Neither did we take into consideration information on the usage of medications. Our results should be confirmed in a larger sample size study involving patients with exudative and atrophic AMD as well as including usage of medication. Ideally patients should be followed up in order to find which form of AMD (wet or dry) will manifest in later years.

CONCLUSIONS

To the best of our knowledge, this is the first study to examine *CYP2C8* rs10509681 and *CYP2C8* rs11572080 genotype frequencies in patients with early AMD. While we could not find differences in genotype frequencies between the healthy controls and patients with early AMD, we think that larger and detailed studies including more aspects of analysis, such as medications and lifestyle, might still elucidate the role of *CYP2C8* in the development of AMD.

The *CYP2C8* gene polymorphisms we examined are only part of studies (18, 26) performed at our laboratory to better understand the roles of genetic markers in AMD development.

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CYP2C8 RS10509681 IR RS11572080 POLIMORFIZMŲ SĄSAJOS SU AMŽINĖS GELTONOSIOS DĖMĖS DEGENERACIJOS PASIREIŠKIMU

Santrauka

Įvadas. Amžinė geltonosios dėmės degeneracija (AGDD) – dažniausiai pasitaikanti negrįžtanti aklumo priežastis išsivysčiusiose šalyse. Pradiniai ligos požymiai yra drūzų formavimasis ir tinklainės pigmentinio epitelio pakitimai. AGDD etiologija ir drūzų formavimosi priežastys nėra visiškai aiškios. Naujausios studijos rodo, kad metaboliniai procesai yra vieni iš svarbiausių AGDD vystymosi priežasčių, o *CYP2C8* genas gali dalyvauti šiame procese. Tyrimo tikslas – nustatyti *CYP2C8* geno (rs10509681 ir rs11572080) polimorfizmų dažnį pacientams, sergantiems ankstyva AGDD ir palyginti rezultatus su kontroline sveikų asmenų grupe.

Metodai. Tyrime dalyvavo 305 pacientai, sergantys pradine AGDD, ir 300 sveikų asmenų. Genotipai išskirti naudojant tikro laiko polimerazės grandinės reakciją.

Rezultatai. *CYP2C8* rs10509681 geno polimorfizmo analizė neatskleidė T/T, T/C ir C/C genotipų pasiskirstymo skirtumo lyginant sergančius AGDD bei sveikus asmenis (83,3; 16,7 ir 0 %, palyginti su 83,7; 15,7 ir 0,7 %, p = 0,343). *CYP2C8* rs11572080 geno polimorfizmo analizė taip pat neatskleidė statistiškai reikšmingų C/C, T/C ir T/T genotipų pasiskirstymo lyginant AGDD sergančius ir kontrolinės grupės sveikus asmenis (84,9; 15,1 ir 0 %, palyginti su 82,3; 17,3 ir 0,3 %, p = 0,447).

Išvados. Palyginę *CYP2C8* geno (rs10509681 ir rs11572080) polimorfizmų genotipų pasiskirstymą sergančių pradine AGDD ir kontrolinėje sveikų asmenų grupėse, statistiškai reikšmingų skirtumų nenustatėme.

Raktažodžiai: amžinė geltonosios dėmės degeneracija, citochromas P450, rs10509681, rs11572080, genų polimorfizmai