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Review

Genetic factors associated with the development of age-related macular degeneration

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ABSTRACT

Age-related macular degeneration (AMD) affects the macula and is the leading cause of significant and irreversible central visual loss. It is the most common cause of visual loss in people aged more than 60 years. This disease affects 2.5 million individuals in Europe. AMD is caused by both environmental and genetic factors. Numerous risk factors have been reported, but the pathogenesis of AMD is complex and fairly understood. Age, female gender, obesity, race, education status, family history, hyperopia, iris color, cigarette smoking, previous cataract surgery, history of cardiovascular and cerebrovascular disease, diabetes, sunlight exposure and many other factors have been shown to be associated with AMD development. Scientific evidence shows that genes may play a role in the development of nearly 3 out of 4 cases of this devastating eye disease. The genes that have been shown to be associated with AMD are genes encoding complement system components such as CFH, C2, C3, CFB, and other.

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1. Introduction

Age-related macular degeneration (AMD) is referred to aging changes without any other obvious precipitating cause that occur in the central area of the retina (macula) in people aged 55 years and more [1]. Impairment of sight and blindness are debilitating and are among the three most feared medical conditions, after cancer and cardiovascular disease [2]. In developed countries, AMD is the most common cause of visual loss in persons aged more than 60 years [3]. More than 30% of adults >75 years-of-age have this disease; in ~6%–8% of these individuals, the disease progresses, causing the most severe degree of visual loss [4]. The prevalence of early AMD increased

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from 1.3% ± 0.3% per subject in the 30-year-old to 40-year-old group, to 3.6% ± 0.5% in the 41-year-old to 50-year-old group, to 7.9% ± 0.9% in the 51-year-old to 60-year-old group, to 10.0% ± 1.1% in the 61-year-old to 70-year-old group, to 8.3% ± 0.2% in the 71-year-old to 80-year-old group, and to 8.0% ± 5.5% in the ≥81-year-old group [5].

AMD is the third leading cause of blindness globally following cataract and glaucoma and it accounts for 8.7% of all blindness cases [6]. In Lithuania, AMD-related blindness accounted for 13.8% and took the second place in 2002 (Lithuanian Medical Social Expertise Commission). The number of AMD-affected people in the developed countries is increasing dramatically. In 2014, Wong et al. published a systematic literature review that aimed to estimate the number of people who will be affected by AMD in the future [7]. This study showed that the prevalence of any AMD was higher in Europeans than Asians and Africans (12.3% vs. 7.4% and 7.5%, respectively). Also, this study reported that the number of persons with AMD will globally increase to 196 million by 2020 and will reach 288 million by 2040 [7].

It is thought that AMD has a multifactorial etiology, the development of which may be caused by interrelation of environmental and body peculiarities; also genetic factors have an impact.

The aim of our article was to review literature, disclose the present view on the pathogenesis and classification of AMD, and reveal factors, especially genetic association, prognosis of the development of this disease.

2. Pathophysiology of age-related macular degeneration

Pathological changes in the macula, a special area of the retina, are associated with the development of AMD. The center of the macula is called the fovea and it contains a huge concentration of photoreceptors with cone cells, responsible for visual acuity and color perception, dominating (up to 200 000 cells/mm^2) [8,9]. The parafoveal area is a region, where rode cells dominate, surrounding the fovea and permitting night vision. In the early stages of AMD, photoreceptors are mostly damaged in the parafovea [10].

Macular degenerative changes occur due to modification of the retinal pigment epithelium and drusen formation in the Bruch membrane, which consists of the retinal pigment epithelium and the choroidal choriocapillary layer. Drusen are extracellular small nodule-shape deposits, made of phospholipids, collagen, and neutral lipids [11]. Also, drusen contain zinc, carbohydrates, and at least 129 different proteins, including apolipoproteins (e.g., apoE, apoB) and excluding structural extracellular matrix. Approximately 30% of the drusen, with a core diameter of 15 μm, consist of nonesterified cholesterol, nonfibrillar amyloid, and peanut agglutinin-binding carbohydrates [11]. These cores may represent nucleation sites for following deposition. Their accumulation alters the delivery of oxygen and nutrients, leading to lesions in the retinal pigment epithelium and a progressive degeneration of photoreceptors, while visual function impairment is associated with the amount of damaged photoreceptors [8].

Histologically drusen are divided into two types: soft and hard. Soft drusen are large, diffuse and composed of an amorphous, granular, and loose material with poorly defined borders [11]. Soft drusen, the main component of basal linear deposit is membranous debris, containing coiled membranes and vesicular outlines of putative retinal pigment epithelium origin. The deposit composition is solid neutral lipid-rich particles. These drusen can form exudative macular degeneration and later can induce the detachment of the neuroepithelium. If the process progresses, new vessel will grow, leading to exudative hemorrhage. Hard drusen are small, distinct, hemispherical, or round-shaped with well-defined borders. Druse composition is solid and hyalinized [11]. They have decreased RPE coverage, consistent with aberrant expression of amyloid A and vitronectin over small drusen. Usually, hard drusen consists of cholesterol, nonfibrillar amyloid, calcifications. Some of them may content nonesterified cholesterol-rich core, and some identified by more shells, which are rich in apoE, apoC-I, and esterified cholesterol [11]. Hard drusen can cause atrophy of the retinal pigment epithelium and the choriocapillary layer [8,9].

3. Classification of age-related macular degeneration

AMD is commonly categorized into early and late forms [8,11]:

- Early AMD is described by the presence of a large number of deposits known as drusen (≤10), which appear below the retinal pigment epithelium and causing more or less pigmentation areas called hyperpigmentation or hypopigmentation. The pigmentation regions are generally diffused [8,11].
- Late form of AMD is classified into dry (with geographic atrophy of the retinal pigment epithelium with the lack of neovascularization areas) and wet types (or exudative; with new blood vessel formations in choroid, called the choroidal neovascularization areas, further leading to the formation or the disciform scars) [8]. The wet type is the heavier form of the disease than the other types [11]. It causes severe damage to the retina and more frequently leads to devastating consequences such as vision loss [8].

4. Risk factors

Epidemiological studies have shown a complex interplay among genetic predisposition, systemic factors, lifestyle and environmental risk factors associated with the risk of AMD development. Age is one of the highest and invariable factors; persons aged between 60 and 80 years are at a 3-fold greater risk of developing advanced AMD compared with those younger than 60 years [12]. Smoking is another significant and modifiable factor. A lot of studies have shown the influence of smoking on AMD formation and have demonstrated that previous and current smokers are inclined to develop AMD at least 5–10 years earlier than nonsmokers [13]. Other factors implicated in the development of AMD are gender, family predisposition, color of the iris, ethnicity, sunlight exposure, body mass index, eating habits, oxidative stress, inflammation and increased levels of inflammatory marker in blood, low antioxidant levels in blood

and diet, cataract and its operation. All these factors considerably affect individual risk.

Age is the most significant risk factor for AMD development. Disease prevalence for late AMD can peak near 10% in persons older than 80 years [14]. The prevalence of late AMD is 1.4% (95% CI, 1.0%–2.0%) at the age of 70 years, rising to 5.6% (95% CI, 3.9%–7.7%) at age of 80 and 20% (95% CI, 14%–27%) at age of 90 [15]. Gender is the second important factor for AMD development: women are at potentially higher risk of neovascular AMD than men [15]. Family history is also a major risk factor for AMD [16,17]. The meta-analysis of the prospective cohort and cross-sectional studies suggested that darker iris pigmentation (brown vs. blue eyes) was protective, but the overall results were not significant (OR = 0.88; 95% CI, 0.65–1.17 cross-sectional studies and RR = 0.98; 95% CI, 0.72–1.32 for prospective studies) [18]. Wong et al. found a higher prevalence of early and any AMD in Europeans than Asians (early: 11.2% vs. 6.8%, Bayes factor 3.9; any: 12.3% vs. 7.4%, Bayes factor 4.3), and early, late, and any age-related macular degeneration to be more prevalent in Europeans than in Africans (early: 11.2% vs. 7.1%, Bayes factor 12.2; late: 0.5% vs. 0.3%, 3.7; any: 12.3% vs. 7.5%, 31.3) [7]. There was no difference in the prevalence between Asians and Africans (all Bayes factors <1) [19]. Europeans had a higher prevalence of geographic atrophy subtype (1.11%; 95% CI, 0.53%–2.08%) than Africans (0.14%, 0.04%–0.45%), Asians (0.21%, 0.04%–0.87%), and Hispanics (0.16%, 0.05%–0.46%) [7]. Among geographical regions, cases of early and any AMD were less prevalent in Asia than in Europe and North America (early: 6.3% vs. 14.3% and 12.8% [Bayes factor 2.3 and 7.6]; any: 6.9% vs. 18.3% and 14.3% [3.0 and 3.8]) [7]. Regarding sunlight as risk factors for AMD, controversial results have been reported: one study found no association between AMD and sun exposure or related factors except for the suggestion of an association between sunburn prone skin type and geographic atrophy, which reached borderline significance [19], while another study found that AMD was probably related to visible radiation especially blue light [20]. Cigarette smoking increases AMD risk. Current smoking was associated with an increased risk of transitioning from minimal to moderate early AMD [21]. Higher systolic blood pressure (OR = 1.06; 95% CI, 1.01–1.12 per 5 mmHg), overweight (OR = 2.87; 95% CI, 1.13–7.29), and obesity (OR = 2.92; 95% CI, 1.06–8.03), physical exercise duration (OR = 0.41; 95% CI, 0.18–0.96 for 30 min or more compared with less) and frequency (OR = 0.46; 95% CI, 0.23–0.92 for weekly or more often compared to less) were associated with late AMD in women only [22]. Also the prevalence of AMD is significantly higher in patients with myocardial infarction than in a random sample of the population [23]. Increased intake of fish reduced the risk of AMD, particularly for 2 or more servings per week (P trend = 0.04). Dietary omega-3 fatty intake was inversely associated with AMD (OR = 0.55; 95% CI, 0.32–0.95) comparing the highest vs. lowest quartile. Reduction in risk of AMD with higher intake of omega-3 fatty acids was seen primarily among subjects with low levels (below median) of linoleic acid intake, an omega-6 fatty acid (P trend < 0.001) [24]. Oxidative stress is believed to be a major mediator of the effect of age because mitochondrial oxidation is impaired with aging and oxidative damage is widely observed. Oxidative stress and the production of reactive oxygen species seem to play a pivotal role in AMD pathogenesis [25]. It is known that the macula receives the highest blood flow of any tissue in the body when related to size, and anything that can reduce the rich blood supply can cause hypoxia, malfunction, or disease. Oxidative stress can affect both the lipid rich retinal outer segment structure and the light processing in the macula [25]. The levels of inflammatory markers, such as serum high-sensitivity C-reactive protein, tumor necrosis factor-α receptor 2, interleukin-6, and soluble vascular cell adhesion molecule-1, in blood were moderately related associated to the 20-year cumulative incidence of early AMD independent of age, smoking status, and other factors [26]. It is not known whether these associations represent a cause and effect relationship or whether other unknown confounders accounted for the findings. Even if inflammatory processes are a cause of early AMD, it is not known whether interventions that reduce systemic inflammatory processes will reduce the incidence of early AMD [26]. More recently, the data from the Age-Related Eye Disease Study concluded that cataract surgery was safe in the setting of dry AMD and did not accelerate progression to advanced sight threatening forms of AMD [27] and phacoemulsification surgery significantly improved vision in patients with neovascular AMD, with no increased need for anti-VEGF injections to keep the macula dry postoperatively [28]. Levels of serum vitamin D are inversely associated with early, but not advanced, AMD. Consistent use vs. non-use of vitamin D from supplements was inversely associated with early AMD only in individuals who did not consume milk daily [29]. Increased blood levels of homocysteine are associated with increased risk of AMD [30].

Not only environmental factors, but also genetic ones, have been reported to be associated with the development of AMD [31]. Over the past decade, more and more researchers focused their attention on detecting the genes, genetic components, which are concerned with the development of AMD. Familial studies have shown that family members of individuals with AMD are at a greater risk of developing the disease comparing to individuals having no family history of the disease [32]. Some twin studies have demonstrated pretty higher accordance rates between monozygotic twins as compared to accordance between dizygotic twins [33].

5. Genes associated with age-related macular degeneration

Genetic studies have shown that numerous genes may be related to age-related macular changes. Some strategies have been attempted to determine the exact genomic regions affected during AMD pathogenesis. The Retina International Database indicates 16 genes that have already been determined to have a link to AMD risk [34]. Complement factor H (*CFH*) was the first significant gene found to be related to AMD by a genome-wide association study. Complement factors B (*CFB*), 2 (*C2*), and 3 (*C3*) are other important genes highly associated with the risk of AMD development [35,36]. The second major locus of the risk of AMD development is linked to genes *HTRA1* and *ARMS2* [37]. In 2013, a genome-wide association study identified 7 new loci near genes *COL8A1-FILIP1L*, *IER3-DDR1*, *SLC16A8*, *TGFBR1*, *RAD51B*, *ADAMTS9*, and *B3GALTL* [38]. Eventually, our search combining all resources revealed 36 genes associated with AMD development (Table).

Table – Genes associated with the risk of age-related macular degeneration.

	Gene	Name	Gene locus	Function	Variant/DNA marker	References
1	*ABCA1*	ATP-binding cassette, sub-family A, member 1	1p22	Molecule transport across cell membranes	rs1883025	[39,40]
2	*ABCA4*	ATP-binding cassette, sub-family A (ABC1), member 4	1p22		rs1800553, rs1800555	[41,42]
3	*ADAMTS9*	ADAM metallopeptidase with thrombospondin type 1 Motif, 9	3p14.1	Regulation of angiogenesis suppression and organ shape during development	rs6795735	[38]
4	*ARMS2*	Age-related maculopathy susceptibility 2	10q26	Unknown function, gene was found first in placenta and is located in the retina	rs10490924	[43]
5	*APOE*	Apolipoprotein E	19q13.2	Lipid and cholesterol transport and catabolism	rs4420638	[38,42,44]
6	*B3GALTL*	Beta 1,3-galactosyltransferase-like	13q12.3	Glycosylation pathway	rs9542236	[38]
7	*CETP*	Cholesteryl ester transfer protein	16q21	Transport of cholesterol	rs3764261	[40,45]
8	*CFB*	Complement factor B R32Q	6p21.3	Alternative complement activation pathway	rs4151667, rs641153	[36,46]
9	*CFH*	Complement factor H Y402H	1q32	Inhibitor of alternative complement pathway	rs1061170	[46–48]
		Independently associated single nucleotide polymorphism (SNP) variant within intron 14 of CFH	1q32		rs10737680, rs1410996	[46,48]
10	*CFHR1*	Complement factor H-related 1	1q31-q32	Possible overlapping function with CFH, complement regulation	rs121913059	[49]
11	*CFHR3*	Complement factor H-related 3	1q31-q32		84-kbp deletion	[49]
12	*CFI*	Complement factor I	4q25	Complement cascade regulation	rs10033900, rs2285714	[50]
13	*COL8A1*	Collagen type VIII, alpha1	3q12.3	Main component in basement membrane of the corneal endothelium	rs13095226	[39,45]
14	*COL10A1*	Collagen, type X, alpha 1	6q21-q22	Produced by hypertrophic chondrocytes and located in mineralization zones of hyaline cartilage	rs3812111	[38]
15	*CX3CR1*	Chemokine (C-X3-C motif) receptor 1	3p21	Leukocytes adhesive and migratory functions	rs3732378	[51,52]
16	*C2*	Complement 2 E318D	9p21	Regulation of complement system activation	rs9332739	[36,46]
17	*C3 R1*	Complement 3 R102G	19p13.3-p13.2	Regulation of complement system activation	rs2230199, rs1047286	[53–55]
18	*C9*	Complement component 9	5p13.1	Regulator of the membrane Attack formation	rs34882957	[56]
19	*DDR1*	Discodin domain receptor tyrosine kinase 1	6p21.3	Cell growth, differentiation and metabolism regulator	rs3094111, rs3130783	[38]
20	*ERCC6*	Excision-repair cross-complementing, group 6	10q11	DNA transcription-coupled excision repair	rs3793784	[57]
21	*FBLN5*	Fibulin 5	14q32.1	The extracellular matrix protein that promotes adhesion of endothelial cells	rs61734479	[58]
22	*FBLN6* or *HMCN1*	Fibulin-6 or hemicentin 1	1q24-q q31.1	Encodes a large extracellular member of the immunoglobulin superfamily	rs743137, rs680638	[59,60]
23	*FILIP1L*	Filamin A interacting protein 1-like	3q12.1	Regulation of antiangiogenic activity in endothelial cells	rs13081855	[38]
24	*FRK*	Fyn-related kinase	6q21-q22.3	Cell growth regulation	rs1999930, rs3812111	[38,61]
25	*HTRA1*		10q26	Cell growth and insulin-like growth factors regulator	rs11200638	[62,63]
26	*IER3*	Immediate early response 3	6p21.3	Regulation of apoptosis	rs3130783	[38]
27	*LIPC*	Hepatic lipase C	15q22	Lipoprotein metabolism	rs10468017, rs493258, rs920915	[45]
28	*QRX/RAXL1*	Retina and anterior neural fold homeobox-like protein 1	19p13.3	Involved in development of the eye; possible modulation of the photoreceptor specific genes expression	Unknown	[64]
29	*RAD51B*	RAD51 homolog B	14q23-q24.2	Pathway of DNA break repair	rs8017304	[38]

Table (*Continued*)

Gene	Name	Gene locus	Function	Variant/DNA marker	References
30 *SLC16A8*	Solute carrier family 16, member 8 (monocarboxylic acid transporter)	22q12.3-q13.2	Transport lactate across cell membrane	rs8135665	[38]
31 *TGFBR1*	Transforming growth factor, beta receptor 1	9q22	Regulation of cell growth and division	rs334353	[38]
32 *TIMP3*	TIMP metalloproteinase inhibitor 3	22q12.3	Extracellular matrix destruction	rs9621532, rs5749482	[40,45]
33 *TLR3*	Toll-like receptor 3	4q35.1	Activation of innate immunity	rs3775291	[65–67]
34 *TLR4*	Toll-like receptor 4	9q32-q33	Activation of innate immunity	rs4986790	[68]
35 *TNFRSF10A*	Tumor necrosis factor receptor super-family, member 10a	8p21	Cell apoptosis regulator	rs13278062	[38]
36 *VEGFA*	Vascular endothelial growth factor A	6p12	Endothelial cell growth regulator; angiogenesis	rs943080, rs4711751, rs833069, rs1413711	[61]

ABCA1. The study by Yu et al. examined 3066 individuals (of them, 221 were categorized as control subjects) and found a strong association between the *ABCA1* gene and medium ($P = 0.0044$) and large ($P = 0.00077$) drusen as well as advanced AMD ($P = 0.0003$) [39].

ABCA4. Mutation in the *ABCR* gene was identified and had susceptibility in people with Stargardt disease. Two most common allele mutations ala1038 to val and gly1961 to glu were found [69]. In 1997, Allikmets et al. found first association of AMD at a significant level in people with AMD [70], and later in 1999, this was confirmed by the study of De La Paz et al. [71]. In 1999, Shroyer et al. performed mutation analysis in one family (family members of three generations) with AMD and Stargardt disease and identified heterozygous mutations in the *ABCA4* gene. The authors proposed that some relatives of patients who carry Stargardt disease might have an increased risk of AMD development [72]. This was also confirmed by another study of the same authors in 2001 [73].

ARMS2. In 2000, Weeks et al. were the first to identify the link between the *ARMS2* gene and susceptibility to AMD [74]. This gene is located on chromosome 10q26. Further research confirmed the association with AMD. In 2005, Rivera et al. identified the T allele of a single-nucleotide polymorphism (SNP) in the *LOC387715* gene (rs10490924), which was related to the risk of AMD [75]. In 2006, the study by Schmidt et al. showed a statistically significant association between *rs10490924* and a greater risk of AMD in smokers [76]. Kanda et al. reported that rs10490924 alone, the 200-kb region on chromosome 10q26, could account for susceptibility to AMD [77].

Fritsche et al. in 2013 confirmed the association between AMD and the T allele of rs10490924 with a P of 4×10^{-540} and OR of 2.76 [38].

The impact of *MMP-2 Rs2285053* ($C \rightarrow T$), *MMP-3 Rs3025039* ($5A \rightarrow 6A$), and *MMP-9 Rs3918242* ($C \rightarrow T$) single nucleotide polymorphism on the development of early AMD was analyzed by the study of Liutkeviciene et al. It showed that only *MMP-9 Rs3918242* ($C \rightarrow T$) single nucleotide polymorphism had a significant influence on the development of AMD, and it was more pronounced at the age of less than 65 years [78].

CFB. Gold et al. studied about 900 individuals with AMD and about 400 controls and reported that 26T-A transversion (resulting leu9 to his variant) and 95G-A transition (resulting arg32 to gln) in the *CFB* gene reduced the risk of AMD development [36]. The findings of the study by Maller et al. carried out in 2006 confirmed the association of leu9-to-his (L9H) and arg32-to-gln (R32Q) in the *CFB* gene with AMD [46].

CFH. Some genome studies on patients with AMD have revealed that polymorphisms in the *CFH* gene can be linked to the development of AMD [36,46]. CFH is a glycoprotein, circulating in blood plasma as an important hematologic component and regulating the activity of the complement system, protecting human cells and tissues from damage caused by pathogens and other dangerous substances during the stimulation of the system. The *CFH* gene is located on chromosome 1q32.

In 2005, Klein et al. performed genome-wide scans of 96 AMD cases and 50 controls to identify polymorphisms associated with AMD. Their analysis showed that an intronic and common variant was strongly related AMD ($P < 1 \times 10^{-7}$) and homozygous individuals harboring the risk allele were more than 7 times more likely to develop AMD (95% CI, 2.9–19) [47]. Another study by Edwards et al. investigated the locus for AMD (*ARMD1*) on chromosome 1q25-31 in 2 independent case–control cohorts: 224 cases and 134 controls. A significant association ($P = 4.95 \times 10^{-10}$) was found within this locus, which has the gene encoding CFH, and the tyrosine-402 → histidine-402 protein polymorphism was associated with a 2.7-fold greater risk of AMD [79]. In the study by Haines et al., Y402H, a common coding variant in the *CFH* gene, was found to increase the risk of AMD by 2.45–5.57 times [80]. In 2009, Bergeron-Sawitzke et al. examined 424 patients with AMD and 215 control individuals who were genotyped for single nucleotide polymorphisms. The study revealed that the GG genotype (rs1410996) of the *CFH* gene was associated with the greatest risk of AMD (OR = 6.6, 95% CI, 3.5–12; $P = 8.7 \times 10^{-11}$) [81].

In 2011, Ho et al. conducted a large-scale study including 2167 people genotyped for *CFH* Y402H or *ARMS2*A69S that aimed to determine whether the consumption of dietary nutrients can reduce the risk of early AMD. The study concluded that high intake of nutrients possessing antioxidant properties was associated with the reduced risk of early AMD [82]. Weismann et al. reported that the *CFH* polymorphism

H402, known for its strong association with AMD, was capable to reduce the ability of the *CFH* gene to bind malondialdehyde, a lipid peroxidation product, that accumulates during numerous pathophysiological processes such as AMD [83]. The study by Hao et al. enrolled 109 AMD patients and 165 AMD-free controls and showed a significant link between *CFH* polymorphisms I62V and Y402H, and susceptibility to AMD in the Chinese population [84]. Carriers of the AA genotype and the A allele of I62V polymorphism were at 3.75-fold (95% CI, 1.70–8.30) and 1.64-fold (95% CI, 1.14–2.36) greater risk to develop AMD. For the Y402H polymorphism, the CT genotype and the C allele were associated with the higher risk of developing AMD (OR = 2.10, 95% CI, 1.04–4.27 and OR = 1.95, 95% CI, 1.02–3.72, respectively). Moreover, carriers of the AT haplotype were more likely than those with the GT haplotype to develop AMD (OR = 3.91, 95% CI = 2.58–5.94) [84].

CFHR1/CFHR3. *CFHR1* and *CFHR3* genes are located on chromosome 1q32 and regulate the activation of complement. The study by Hageman et al. carried out genotyping analyses of patients with AMD and controls and identified a large common deletion (copy number polymorphism 147 [CNP147]) that encompasses both these genes. The authors concluded that the absence of *CFHR1* and/or *CFHR3* might have a protective effect against AMD [85]. Another study showed that persons carrying fewer than 2 copies of CNP147 and haplotype T-G-D were at 1.75-fold (adjusted OR = 0.57; 95% CI, 0.38–0.8; $P = 0.006$) and 4-fold (OR = 0.25, 95% CI, 0.17–0.36; $P = 1.3 \times 10^{-13}$) lower risk of having AMD [86].

Raychaudhuri et al. matched the association of *CFHR1/CFHR3* deletion with AMD. They examined the Y402H allele, using *rs10801555* as a proxy and *rs1410996*, using *rs10737680* as a proxy. It was found that deletion of *CFHR1/CFHR3* and *rs10737680* decreased the risk of AMD, but they were not completely independent, assuming that there can be more variant, which were not yet recognized and can better explain the risk of disease [87].

CFI. The *CFI* gene encodes a complement system protein known as complement factor I. In 2013, van de Ven et al. analyzed and found 2 heterozygous missense mutations in the *CFI* gene: G188A and G119R. It was found the strong linkage to developing of AMD [88]. Especially, those patients who carried G119R mutation had more severe and advanced form of the disease. Also, 192 ancestry- and age-matched controls individuals, carrying the G188A and G119R mutation, did not have any other mutations in the *CFH* gene [88]. In addition, the G119R variant of *CFI* gene was recorded in persons with atypical hemolytic uremia syndrome [89]. Mild renal function decline in AMD-affected patients with G119R change of the *CFI* gene was noted. However, there was no significant difference in renal function between AMD individuals with G119R mutation and without it [90].

CX3CR1. In 2004, Tuo et al. examined 117 individuals with AMD and 276 controls and found that lower CX3CR1 expression was associated with AMD formation [91].

C2. The study involving nearly 900 individuals with AMD and nearly 400 controls showed that the variant of E318D and haplotype H7 in *C2* considerably decreased the risk of developing AMD [36].

C3. It was reported that patients carrying K155Q variant (rs147859257) with the C allele of rs2230199 had an association with high risk of AMD [38]. In 2013, Sedon et al. reported that the allele of the *C3* gene encoding Gln155 (p.Lys155Gln substitution) caused resistance to proteolytic activation in the pathogenesis of AMD [92]. In the same year, the study by Helgason et al. confirmed this rare nonsynonymous SNP in the *C3* gene. It was suggested that this substitution was associated with the reduction of *C3* gene binding to CFH, resulting in resistance to inhibition by this factor that in turn leads to an increase in compliment activation [93].

C9. Recently, a new gene, increasing the risk of AMD, has been identified. In 2013, Seddon et al. performed genotyping of 5115 independent samples and confirmed an association between the allele in the *C9* gene encoding p.Pro167Ser and AMD (joint OR = 2.2; $P = 6.5 \times 10^{-7}$) [92].

ERCC6. Tuo et al. examined a cohort of 460 individuals with advanced AMD and 265 controls and reported that C-6530 > G SNP in the *ERCC6* gene was strongly related to AMD [57].

FBLN5. In 2004, Stone et al. examined 402 individuals with AMD and 429 controls and identified 7 various mutations in the *FBLN5* gene in patients with confirmed AMD diagnosis and small circular drusen [58]. Another study examined 805 AMD-affected patients and 279 control cases and determined 9 *FBLN5* gene mutations to be associated with different phenotypes of AMD and 2 associated with autosomal recessive cutis laxa. *FBLN5* secretion was considerably decreased in cases of 4 AMD and 2 cutis laxa mutations. The findings of this study suggest that some missense mutations related to AMD result in reduced *FBLN5* expression followed by a possible decrease in elastogenesis [94].

FBLN6. The study by Schultz et al. screened 20 candidate genes in the region between LAMB2 and D1S3469. Only one DNA variation in the hemicentin 1 (HMCN1) gene (16263A > G transition in exon 104 producing Gln5345Arg change) on chromosome 1q31 was identified in a large family with AMD [59]. Later, Fisher et al. reported that p.Gln5346Arg mutation, considered as a causal mutation, appeared to be documented at low frequency in the control group. These findings suggested that this polymorphism can provide the linkage to AMD in a small group of individuals, but did not lead essentially to the disease [95].

FRK/COL10A1. In 2011, Yu et al. performed a large meta-analysis of genome-wide association studies in order to identify genetic loci contributing to susceptibility to AMD. This study, besides confirmation of 10 loci previously reported to be associated with AMD, identified two novel susceptibility alleles, one of them being the rs1999930 allele near the *FRK/COL10A1* gene ($P = 1.1 \times 10^{-8}$) [61].

HTRA1. Dewan et al. reported that rs11200638 of the *HTRA1* gene was the major genetic risk factor for the development of wet AMD and individuals carrying the risk genotype were 10 times more likely to develop this form of the disease than their counterparts with the wild-type genome [62]. Later, the *HTRA1* gene (rs11200638) was confirmed to be associated with age-related macular degenerative disease ($P = 6.9 \times 10^{-29}$) [96].

LIPC. In 2013, Lee et al. analyzed 2 independent Caucasian cohorts: one including 1626 individuals with advanced AMD and 859 controls, and another with 2159 patients and 1150 control cases. *rs493258* and *rs10468017*, two promoter variants of the *LIPC* gene, were found to have a link to advanced AMD in the Caucasian population [97].

QRX. Wang et al. investigated 92 cases with AMD; 322, with cone rod dystrophy; 14, with autosomal dominant retinitis pigmentosa; and 14, with autosomal recessive retinitis pigmentosa. There were 3 different heterozygous sequence variants in the *QRX* gene, one of which was found in a 67-year-old patient with AMD, who harbored a heterozygous G-to-A change (CGG to CAG, arginine to glutamine) at codon 87 [64].

TLR3. The study by Yang et al. analyzed associations between the *TLR3* variant *rs3775291* and advanced AMD (geographic atrophy and choroidal neovascularization) and reported that T allele (*rs3775291*) in the *TLR3* gene had a protective effect against geographic atrophy, while none of the *TLR3* variants was found to be associated with choroidal neovascularization [67].

VEGFA. Huang et al. performed a meta-analysis of 9 studies and showed that out of the 4 polymorphisms of the *VEGFA* gene, which were analyzed in this study, rs1413711 and rs833061 were found to be associated with an increased risk of AMD [98].

Other genes. In 2013, Fritsche et al. conducted a genome-wide association study and for the first time identified 7 loci near the genes *ADAMTS9*, *RAD51B*, *COL8A1/FILIP1L*, *IER3/DDR1*, *B3GALTL*, *SLC16A8*, and *TGFBR1*. All these loci were associated with AMD at $P < 5 \times 10^{-8}$ [38]. The study by Whitmore et al. showed lower expression of the *ADAMTS9* gene in samples high-risk CFH genotypes. *ADAMTS9* has an influence on angiogenesis by suppressing it. Therefore, a decline in *ADAMTS9* expression can be associated with a greater risk of developing AMD formation [99].

6. Concluding remarks

Numerous genes have been implicated in the pathogenesis of AMD. The genes associated with the complement system (*CFH*, *CFB*, *CFI*, *C3*) confer a higher risk of developing AMD. Moreover, understanding of genetic predisposition and the role of nongenetic environmental factors, such as diet, smoking, and other factors allows identifying biochemical processes for a greater part of AMD patients and essentially increases the opportunity to predict the risk of this disease and to develop new therapies. Despite current advanced technologies, the factors influencing the development of early and late AMD remain are still not entirely clear.

Conflict of interest

The authors state no conflict of interests.

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