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Review

Genomic aspects of age-related macular degeneration

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ABSTRACT

Age-related macular degeneration (AMD) is a major late-onset posterior eye disease that causes central vision to deteriorate among elderly populations. The predominant lesion of AMD is the macula, at the interface between the outer retina and the inner choroid. Recent advances in genetics have revealed that inflammatory and angiogenic pathways play critical roles in the pathophysiology of AMD. Genome-wide association studies have identified *ARMS2/HTRA1* and *CFH* as major AMD susceptibility genes. Genetic studies for AMD will contribute to the prevention of central vision loss, the development of new treatment, and the maintenance of quality of vision for productive aging.

Contents

1. Introduction

Age-related macular degeneration (AMD) is a common eye disease that leads to the deterioration of the central vision in elderly people, particularly in those over 60 years of age. This disease causes damage to the macula, which is a small spot near the center of the retina (2 mm in diameter). When the structure of eyeball is likened to that of a traditional camera, the retina corresponds to a film and the subretinal pigment-rich tissue, the choroid, corresponds to a camera obscura. The macula would be considered as a special film with intense light sensitivity, as it is the particular region of the retina due to the high density of cone photoreceptors that are responsible for the sharpness of the central vision and color vision.

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AMD is one of the most frequent diseases for acquired vision loss and blindness in developed countries. Because of the exponential growth of the aging population, the prevalence of AMD is increasing. A meta-analysis by the Eye Diseases Prevalence Research Group estimated that the overall prevalence of AMD in the population of the United States 40 years and older in 2000 was estimated to be 1.5%, with 1.75 million individuals affected by the disease [1]. AMD is far more prevalent among whites than among blacks [1,2]. A recent meta-analysis of 3 large population-based cohort studies within the Three Continent AMD Consortium, using data for 6,953 participants from the Beaver Dam Eye Study (BDES) in the United States, Blue Mountains Eye Study (BMES) in Australia, and Rotterdam Study (RS) in the Netherlands, the average 5-year incidences of early AMD were 8.1%, 15.1%, and 13.0% in the BDES, BMES, and RS, respectively [3]. The average 5-year incidences of late AMD were 1.2%, 1.7%, and 1.7% in the BDES, BMES, and RS, respectively. A meta-analysis in Asians aged 40–79 years showed that age-specific prevalence of late AMD in Asians was similar to that in Europeans, whereas early AMD was less common in Asians (6.8%) than in Europeans (8.8%) [4]. Based on a recent systemic review and meta-analysis, 8.7% of the worldwide population has AMD, and the projected number of people with the disease will be ~196 million in 2020, increasing to ~288 million in 2040 [5].

From genomic aspects, AMD has been paid particular attention by researchers involved in human genetics as well as those involved in ophthalmology. Disease-susceptible genes including such as complement pathway, proteases, and lipid metabolism have been successfully identified genetic analyses including genome-wide association studies (GWASs) [6]. As elucidated by these studies, it is now assumed that both genetic and nongenetic factors coordinately contribute to the development and progression of AMD. Here we overview the genomic aspects of AMD that have been extensively studied since the beginning of this century. We also discuss the non-genetic factors that modify the effects of genetic factors on the pathophysiology of AMD.

2. Pathology and etiology

AMD is pathologically derived from the interface between the retina and the choroid in the macular region. The chorioretinal interface consists of the retinal pigment epithelium (RPE) in the outer layers of the retina and Bruch's membrane, the inner extracellular matrix layer of the choroid. A debris-like extracellular deposit, designated as drusen, often accumulates between the RPE and Bruch's membrane with aging. In the RPE, intracellular lysosomal lipofuscin, which is a nondegradable debris that composed of a mixture of different fluorophores, often aggregates with age [7]. The term lipofuscin was originated from the Greek "lipo" (for fat) and Latin "fuscus" (for dark) [8]. Although the nature of lipofuscin fluorophores has not been fully characterized, autofluorescent compounds derived mainly from vitamin A have been identified in RPE cells as byproducts of the visual cycle. One of the vitamin A-derived fluorophores is N-retinyl-N-retinylidene ethanolamine (A2E), which has the structure of a Schiff base that is generated by reactions between retinaldehyde (all-*trans*-retinal) and phosphatidylethanolamine, both are components of photoreceptor outer segment membranes [9,10]. Lipofuscin has been shown to mediate light-induced damage via radial oxygen species (ROS) and to be toxic to RPE cells [11–14]. A2E might also enhance the effects of moderate mitochondrial defects, impairing oxidative phosphorylation-dependent energy production and phagocytosis of the photoreceptor outer segment in aging RPE cells [15]. Similar to AMD, analogous lipofuscin-like proteins also interact with mitochondrial dysfunction in other neurodegenerative diseases, such as amyloid beta in Alzheimer's disease, parkin in Parkinson's disease, and superoxide dismutase (SOD) 1 in amyotrophic lateral sclerosis, and Huntingtin in Huntington's disease [16]. It has been speculated that lipofuscin in RPE and drusen on Bruch's membrane might interact with each other, although their precise relationship remains to be studied. Confluent drusen at the chorioretinal interface could activate the complement cascade and induce retinal inflammation, leading to the pathogenesis of early AMD. These age-related changes at Bruch's membrane may also be involved in the pathogenesis of other retinal diseases including retinitis pigmentosa and Stargardt disease [17,18]. Overall, the inflammation at the chorioretinal interface is likely a primary event for the onset of AMD, although aging itself is the major risk factor for the disease.

Impaired secretion of proteins by the RPE from both apical and basolateral sides will contribute to the pathogenesis of AMD, as recently reviewed by Dr. Paraoan and her colleagues [19]. In particular, cystatin C, a cysteine proteinase inhibitor, is one of the most abundantly expressed and basolaterally secreted proteins in the RPE [20,21]. Reduced secretion of cystatin C in brain may contribute to the development of Alzheimer's disease [22]. A homozygous genotype for mutant variant B of cystatin C has been shown to correlate with an increased risk of developing exudative AMD, with a relatively early onset [23].

In advanced stages of AMD, the disease can be roughly categorized into following 2 phenotypes: "atrophic AMD"/"dry AMD", with the presence of drusen and thinning of the macula because of RPE cell atrophy, or "neovascular AMD"/"exudative AMD"/"wet AMD", with choroidal neovascularization (CNV) that is new blood vessels underneath the retina (Fig. 1). In wet AMD, at least 3 subtypes are sub-categorized: typical AMD (tAMD), polypoidal choroidal vasculopathy (PCV), and retinal angiomatous proliferation (RAP). PCV was first defined by Dr. Yannuzzi in 1982, with a phenotype of subretinal vascular lesions associated with serous and hemorrhagic detachments of the RPE [24,25]. PCV was initially considered a distinct abnormality of the choroidal vasculature found in the peripapillary area. Currently PCV is considered a subtype involved in wet AMD [26]. The prevelance of PCV in Asians is higher than that in Caucasians. For example, PCV is observed in 48% of Japanese patients whereas in 9% French patients [27]. RAP is usually described as "deep retinal vascular anomalous complex" and "retinal–choroidal anastomosis" [28]. According to a classification by Dr. Gass and its modification by Dr. Freund, 3 types of posterior chorioretinal neovascularization are defined in terms of its anatomical relationship to RPE layer: type 1 neovascularization as fibrovascular tissue posterior to RPE, type 2 neovascularization as fibrovascular complex that lies anterior to the RPE, and type 3 as intraretinal neovascularization, putatively occurred in RAP lesions [29,30].

In the pathogenesis of AMD, macrophages play a critical role in inflammatory lesions. Both bone marrow-derived immigrant macrophages and local microglia-derived macrophages from the inner retina are involved in the phagocytosis of apoptotic photoreceptors and the clearance of cell debris [31]. Although the specific roles of macrophages at different disease stages remain controversial, both pro-inflammatory M1 macrophages and anti-inflammatory M2 macrophages may be involved in the development and progression of AMD. Recent studies have revealed that macrophages recruited under the retina at the initial stage of AMD exhibit a pro-inflammatory M1 phenotype [32–34]. T cells may also be involved in the pathology, as shown by a study of carboxyethylpyrrole-immunized mice, which exhibit AMD-like pathology [33]. Human histopathological studies suggest that M2 macrophages are likely activated in later AMD stages rather than in early stages [35,36]. Thus, immune responses evoked by drusen-induced inflammation likely play a central role in the pathogenesis of AMD. The mechanism seems

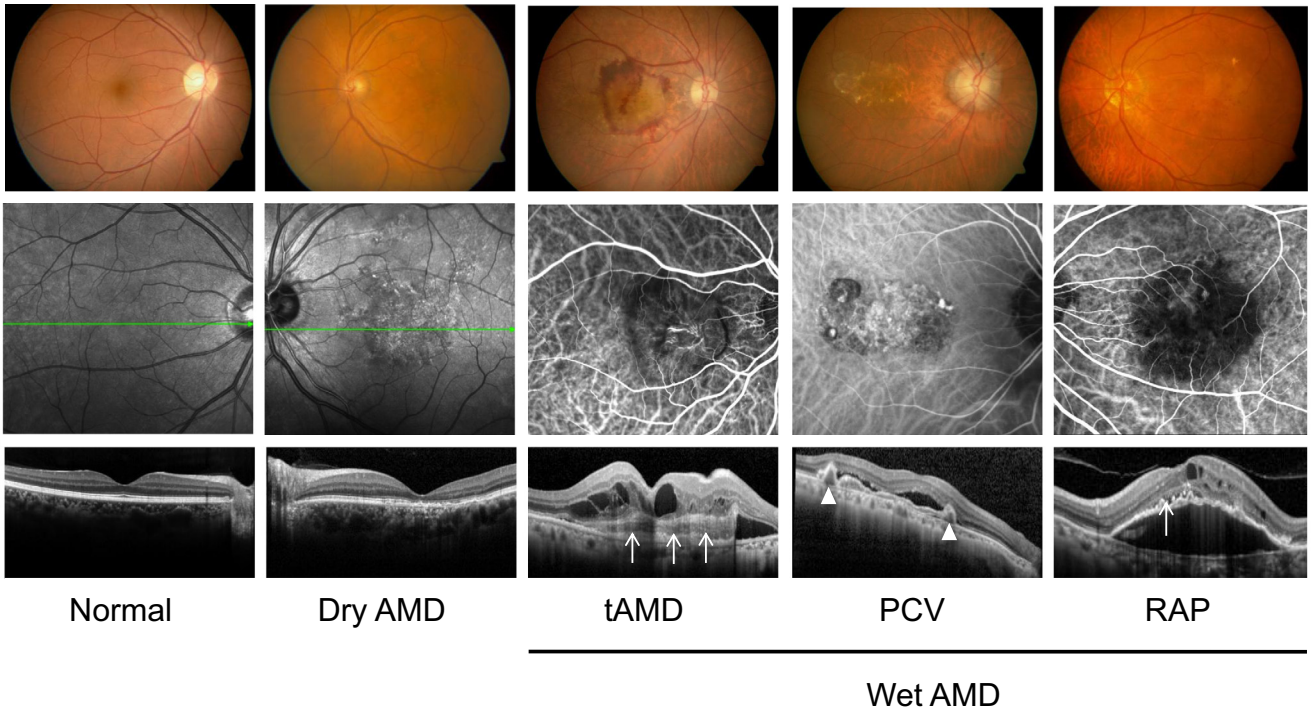

Fig. 1. Clinical features of age-related macular degeneration (AMD). Top panels: Fundus photographs of the retina of a normal individual and patients with dry AMD or wet AMD. Wet AMD is sub-categorized as typical AMD (tAMD), PCV (polypoidal choroidal vasculopathy), and RAP (retinal angiomatous proliferation). Subretinal hemorrhage is remarkable in the retina with tAMD. Middle panels: Corresponding red-free fundus photographs of the retina of a normal individual and a patient with dry AMD (left 2 panels) and indocyanine green (ICG) angiography of the retina of patients with wet AMD (right 3 panels). The accumulation of multiple drusen is shown in the central retina with dry AMD. ICG angiography shows ICG dye leakage from choroidal neovascularization in the eye with typical AMD, or ICG dye pooling in choroidal vascular polyps together with abnormal vascular network in the eye with PCV. Bottom panels: Corresponding optical coherent tomography (OCT) of the central retina (macula). OCT shows the photoreceptor cell atrophy, the disruption of the junction between inner segments (ISs) and outer segments (OSs) of the photoreceptors, and the presence of drusen underneath the retinal pigment epithelium (RPE) layer of the retina in the eye with dry AMD. The complex of choroidal neovascularization (arrows) and serous retinal detachment are shown in the eye with tAMD. Choroidal vascular polyps (arrowheads) and serous retinal detachment is shown in the eye with PCV. In the eye with RAP, intraretinal (arrow) and subretinal neovascularization are shown.

has many similarities with that of atherosclerosis. Of note, many complement proteins have been identified in drusen and in atherosclerotic plaque, suggesting the activation of the complement pathway within the deposits. Vitronectin, amyloid component, fibrinogen, clusterin, and tissue inhibitor of metalloproteinase 3 (TIMP-3) are molecular constituents of both drusen and atherosclerotic plaques [34].

3. Genetic factors for AMD

Understanding of the genetics of AMD has advanced considerably during the last decade. Previously, limited information on AMD genetics was available from familial aggregation and twin studies, and a small number of disease susceptibility genes involved in the pathogenesis of AMD had been identified [37–42]. Family-based linkage studies revealed 2 strong susceptibility loci on chromosomes 1 and 10, corresponding to complement factor H (*CFH*) and *ARMS2*/*HTRA1* loci [43–47]. Other genomic regions have been also shown to have weak linkage with AMD. A breakthrough in AMD genetics has been achieved with GWAS, and informative single nucleotide polymorphisms (SNPs) have been validated within a short period of time. In particular, several major AMD susceptibility genes have been identified, including *CFH* on chromosome 1q32 [48–52], *LOC387715*/*ARMS2* on 10q26 [53–57], *HTRA1* on 10q26 [58–61], and *C2*/*BF* on 6p21 [62,63]. Recently, GWASs in large cohorts and deep sequencing studies by next-generation technologies have identified several additional genes as risk factors for AMD susceptibility.

3.1. Complement factor genes

Complement pathway activation is one of the major signal transduction pathways involved in AMD pathogenesis. Namely, uncontrolled complement proteins promote various reactions, including leukocyte accumulation, generation of reactive oxygen species, drusen formation, membrane attack complex (MAC)-induced RPE cell lysis, and elevation of vascular endothelial growth factor (VEGF), which leads to choroidal neovascularization [6]. For general information on the complement system, an excellent review by Dr. Lambris and his colleagues provides a complete overview of the structure and function of the system [64]. In the alternative pathway, a small fraction of the central molecule C3 molecules are hydrolyzed to $C3_{H2O}$. The factor B protease, encoded by CFB, binds $C3_{H2O}$ and is cleaved by factor D, generating C3 convertase ($C3_{H2O}$ Bb). C3 convertase activates complement by cleaving C3 into its active fragments, C3a and C3b. Complement factor H, encoded by CFH, mainly acts on C3 convertases in the alternative pathway, either competitively removing Bb from the C3bBb complex (decay acceleration) or serving as a cofactor for the complement factor I (CFI)-mediated degradation of C3b, while stabilizing the overall domain arrangement of C3b [65].

CFH is a member of the Regulator of Complement Activation (RCA) cluster. The 155-kDa protein, which circulates in bloodstream as a secreted glycoprotein, plays an inhibitory role in the regulation of the alternative complement pathway [66]. CFH protein contains 20 structurally similar complement-control protein (CCP) domains [67]. The finding, through a GWAS, that *CFH* is a major AMD susceptibility locus is a remarkable milestone in

Table 1
Major AMD susceptibility genes.

Gene locus	Chromosome	Gene name	Index SNP-risk allele[a]	Context	Risk allele frequency[b]			Gene ontology & function	References
					CEU	JPT	YRI		
ARMS2	10q26.13	Age-related maculopathy susceptibility 2	rs10490924-T (69Ser)	Missense (A69S)	0.199	0.384	0.257	Retina homeostasis	[54,63,120,126,205]
HTRA1	10q26.13	HtrA serine peptidase 1	rs11200638-A	5′ up (0.5 kb)	0.200	0.368[c]	0.288	Proteolysis, regulation of cell growth, negative regulation of BMP/TGF-beta receptor signaling pathway	[57–61]
CFH	1q32	Complement factor H	rs10737680-A	Intron	0.580	0.552	0.425	Regulation of complement activation	[121,126]
			rs800292-A (62Ile)	Missense (I62V)	0.217	0.401	0.814		[51,79,115]
			rs1061170-C (402His)	Missense (Y402H)	0.286	0.057	0.272		[48–52,63,120,205]
			rs1410996-C	Intron	0.592	0.602	0.342		[63,79,115,120]
C2	6p21.3	Complement component 2	rs9332739-G (318Glu)	Missense (E318D)	0.933	0.977	0.983	Complement activation	[62,63,121,205]
			rs429608-G (SKIV2L intron)	Intron	0.858	0.884	0.862		[121,126]
CFB	6p21.3	Complement factor B	rs641153-G (32Arg)	Missense (R32Q)	0.942	0.898	0.883	Complement activation	[62,63,120,205]
C3	19p13.3-p13.2	Complement component 3	rs2230199-G (102Gly)	Missense (R102G)	0.175	0.000	0.008	Complement activation	[120,121,126,127,205]
TIMP3	22q12.3	TIMP metallopeptidase inhibitor 3	rs5749482-C	5′ up (137 kb)	0.108	0.744	0.508	Metalloendopeptidase inhibitor activity	[126]
			rs9621532-C	5′ up (112 kb)	0.062	0.017	0.102		[120,121,205]
SYN3	22q12.3	Synapsin III	rs5749482-C	Intron	0.108	0.744	0.508	Metabolic process, neurotransmitter secretion	[126]
APOE	19q13.2	Apolipoprotein E	rs4420638-A	3′ down (14 kb)	0.840[d]	0.897[d]	0.760[d]	Lipid binding, catabolism of triglyceride-rich lipoprotein constituents, cholesterol/fatty acid homeostasis	[126,127]
APOC1	19q13.2	Apolipoprotein C-I	rs4420638-A	3′ down (5 kb)	0.840[d]	0.897[d]	0.760[d]	Negative regulation of lipoprotein lipase activity and cholesterol transport	[126,127]
CETP	16q21	Cholesteryl ester transfer protein, plasma	rs1864163-G	Intron	0.741	0.872	0.716	Cholesterol/lipid transporter activity	[126]
			rs3764261-A	5′ up (2.5 kb)	0.345	0.198	0.288		[205]
VEGFA	6p12	Vascular endothelial growth factor A	rs943080-T	3′ down (72 kb)	0.473	0.669	0.898	Angiogenesis, VEGF-activated neuropillin signaling pathway	[126,127]
			rs4711751-T	3′ down (74 kb)	0.458	0.717[e]	0.975		[205]
TNFRSF10A	8p21	Tumor necrosis factor receptor superfamily, member 10a	rs13278062-T	5′ up (0.3 kb); ncRNA (LOC389641) exon	0.473	0.407	0.116	TRAIL-activated apoptotic signaling pathway/activation of NF-kappaB-inducing kinase activity	[122,126]
COL8A1	3q12.3	Collagen, type VIII, alpha 1	rs13081855-T	Intron	0.058	0.041	0.036	Angiogenesis/extracellular matrix organization	[120,126,127]
IER3	6p21.3	Immediate early response 3	rs3130783-A	5′ up (62 kb)	0.814	0.680	0.522	Regulation of DNA damage stimulus/ negative regulation of inflammatory response	[126]
DDR1	6p21.3	Discoidin domain receptor tyrosine kinase 1	rs3130783-A	5′ up (77.5 kb)	0.814	0.680	0.522	Extracellular matrix organization/ regulation of cell growth	[126]
SLC16A8	22q12.3-q13.2	Solute carrier family 16 (monocarboxylate transporter), member 8	rs8135665-T	Intron	0.175	0.114	0.375	Leukocyte migration/cellular metabolic process	[126,127]
TGFBR1	9q22	Transforming growth factor, beta receptor 1	rs334353-T	Intron	0.774	0.547	0.805	Angiogenesis/cell motility	[126,127]
LIPC	15q21-q23	Lipase, hepatic	rs920915-C	5′ up (36 kb)	0.500	0.144	0.450	Dual functions of triglyceride hydrolase and ligand/ bridging factor for receptor-mediated lipoprotein uptake	[126]
			rs10468017-T	5′ up (46 kb)	0.310	0.220	0.104		[120,205]
CFI	4q25	Complement factor I	rs4698775-G	3′ down (71 kb)	0.311	0.218	0.009	Regulation of complement activation	[126]
CCDC109B			rs4698775-G	Intron	0.311	0.218	0.009		[126]
RAD51B	14q23-q24.2	RAD51 paralog B	rs8017304-A	Intron	0.628	0.471	0.252	Double-strand break repair via homologous recombination	[126,127]
ADAMTS9	3p14.1	ADAM metallopeptidase with thrombospondin type 1 motif, 9	rs6795735-T	5′ up (32 kb)	0.451	0.791	0.885	Metallopeptidase activity	[126,127]

COL10A1	6q21–q22	Collagen, type X, a 1	rs3812111-T	Intron	0.629	0.789	0.245	Extracellular matrix organization	[126]
			rs1999930-T	3′ down (53 kb)	0.299	0.006	0.009		[205]
B3GALTL	13q12.3	Beta 1,3-galactosyltransferase-like	rs9542236-C	Intron	0.475	0.013	0.158	Protein glycosylation	[126,127]
REST[f]	4q12	RE1-silencing transcription factor	rs1713985-G	Intron	0.102	0.267	0.004	Negative regulation of gene expression/ neurogenesis	[122]

[a] Modified from data in The NHGRI GWAS Catalog (Ref. [203]).
[b] Retrieved from HapMap Project database (Ref. [204]). CEU, European descendant; JPT, Japanese; YRI, Sub-Saharan Afican.
[c] Retrieved from data in Ref. [115].
[d] Retrieved from data in Ref. [137] (East Asian data is substituted for JPT data).
[e] Retrieved from HapMap data of JPT + CHB.
[f] Validated in Japanese.

understanding the genetics of the disease [48]. Several groups independently validated *CFH* as a strong susceptibility locus using case-control cohorts and family-based data set [49–52]. Among several key SNPs in the CFH locus, the Tyr402His (Y402H) polymorphism was the initial focus of attention, especially in Caucasians (Table 1). The amino acid position of Y402H substitution is located in the CCP 7 module of CFH, which plays a role in glycosaminoglycans and sialic acid binding. In homozygotes with the 402HH variant, the levels of C-reactive protein in the RPE-choroid are ~2.5-fold higher than in homozygotes with the 402YY variant [68]. Compared with the 402Y allotype, the AMD-associated 402H allotype interacts less well with binding sites within Bruch's membrane of the macula, where the glycosaminoglycans heparan sulfate and dermatan sulfate play a role in mediating the interaction with CFH [69]. In Asian cohorts, the effect allele frequency of the Y402H SNP in Asians is relatively low (~5% for minor allele frequency) and a number of studies show that the Y402H SNP is marginally associated with typical AMD [60,70–73] and PCV [74,75] among Asian populations. Several studies for Asian cohorts have shown, however, that Y402H SNP can be used as an alternative marker for AMD and PCV in Asians [76–78].

In contrast to the Y402H polymorphism, the CFH Ile62Val (I62V) polymorphism is relevant to AMD susceptibility in both Asians and Caucasians [51,75,79]. The I62V substitution is located in the CCP 2 module. The I62V polymorphism is unique: the Ile62 CFH variant confers strong protection to AMD, as well as atypical hemolytic uremic syndrome (aHUS) and dense deposit disease. The CFH Ile62 variant binds more efficiently to C3b than does CFH Val62 and competes better with factor B in proconvertase formation [80]. An intronic SNP of *CFH*, rs1410996, has been identified as another variant strongly associated with AMD susceptibility in Caucasians [63,81]. The relevance of this SNP to AMD risk has also been shown in Asians [79,82].

A deep sequencing study identified a rare variant of *CFH* encoding the Arg1210Cys substitution [83], which has been implicated in aHUS [84]. The Cys1210 mutation in the CCP 20 module of CFH abrogates C-terminal ligand binding, with defective binding to C3b, C3d, heparin, and endothelial cells, resulting in impaired CFH attachment to host surfaces and reduced complement regulation [84]. Thus, this loss-of-function variant of *CFH* is likely to drive AMD risk.

The contribution of *C2*/*BF* to the pathogenesis of AMD may be more critical in Caucasian populations than in Asian populations. For example, the effect allele frequency of a critical SNP (rs429608) at the *C2*/*CFB* loci is >15% in Caucasian populations while <10% in Asian populations, according to data from the 1000 Genomes Project [85]. Nevertheless, weak associations of *C2*/*CFB* with AMD and PCV have been shown in Asians [86].

In addition to *CFH* and *C2*/*CFB*, several other factors involved in the alternative complement pathway are associated with AMD risk. *CFH* and the closely related genes *CFHR3*, *CFHR1*, *CFHR4*, *CFHR2*, and *CFHR5* within the RCA gene cluster, spanning a range of 355 kb on chromosome 1q23, may have arisen through gene duplication. The genes share extremely high nucleotide sequence similarity. A copy number polymorphism downstream of *CFH* that includes an 86-kb deletion of *CFHR3* and *CFHR1* has been identified as a protective haplotype (ancestral segments of DNA that tend to be inherited as a unit or block) for AMD in Caucasians [87–90]. With regard to the association of the *CFHR3* and *CFHR1* deletion with CFH risk markers, this deletion always occurred on a protective haplotype that spans exon 2 through exon 9 of *CFH*, never on the risk haplotype tagged by the Y402H risk allele [91]. In Asians, the haplotype of the *CFHR3*/*CFHR1* deletion is not polymorphic and may not be substantially associated with the disease [92]. In contrast to its association with the pathogenesis of AMD, the *CFHR3*/*CFHR1* deletion is a risk haplotype for aHUS [93], a condition that results from the abnormal premature

destruction of red blood cells. aHUS is associated with defective complement regulation, including a number of *CFH* mutations [94].

C3 is an acute phase reactant of complement pathways. Synthesis of C3 is induced during acute inflammation. A common functional Arg102Gly (R102G) polymorphism (rs2230199) in *C3* has been associated with AMD in Caucasians [95–98]. The Arg102Gly polymorphism, distinguishable as an electrophoretically fast form of C3, may be a causative SNP for AMD as well as other diseases, including renal transplant survival [99], Chagas disease cardiomyopathy [100], and type II mesangiocapillary glomerulonephritis [101]. The intronic polymorphism rs2241394 is associated with PCV [102] and AMD [103] in Japanese cohorts.

A recent deep sequencing study to the coding regions of AMD-associated genes revealed associations between AMD and rare variants in the complement pathway, including *CFI*, *C3*, and *C9* [104]. The study showed significant associations of AMD with a rare *C3* missense allele encoding the Lys155Gln (K155Q) variant (rs147859257) and with a *C9* allele encoding the Pro167Ser (P167S) variant (rs34882957) [104]. The substitution of Gln for Lys at codon 155 of C3 has been shown to impair C3b regulation by CFI with bound CFH, resulting in increased C3 convertase formation and feedback amplification of the alternative complement pathway. The study also revealed that rare missense *CFI* variants were enriched in AMD cases compared with controls. *CFI* encodes complement factor I, which consists of a heavy chain and a light chain, with a catalytic serine protease domain that cleaves the C3 protein. Many of the rare *CFI* variants, particularly those with loss-of-function mutations, were also found in patients with aHUS, although there was no statistically significant evidence of association with AMD for the individual *CFI* variants assessed in the study [104].

In a conventional sequencing study focusing on *CFI*, a rare, highly penetrant *CFI* variant encoding a Gly119Arg substitution conferred a high risk of AMD [105]. *In vitro* and *in vivo* experiments showed that the human CFI Arg119 mutant protein was expressed and secreted at lower levels than the CFI Gly119 wild-type protein and exhibited reduced activity in regulating vessel thickness and branching in the retina.

3.2. ARMS2/HTRA1 locus

In regard to variations in a locus at chromosome 10q26, it is under debate whether *ARMS2* or *HTRA1* are functionally responsible for AMD susceptibility. The most significantly associated haplotype includes SNP rs10490924 [nonsynonymous change Ala69Ser (A69S)] in *ARMS2* [53–57] and rs11200638 in the promoter region of *HTRA1* (Table 1) [58–61]. Because very high linkage disequilibrium (LD) has been observed in the region, it is rather difficult to determine which susceptibility variants and genes are critical for AMD pathology by genetics alone [106]. The risk allele for rs11200638 was initially shown to be associated with elevated expression levels of its mRNA and protein [59]. Recent studies with a substantial sample number rather show that the AMD-associated variations at 10q26 locus will not significantly affect the expression levels of either *ARMS2* [107] or *HTRA1* [107,108]. In a transgenic study of human *HTRA1* in mouse RPE, nevertheless, increased HTRA1 induces a phenotype of PCV, namely, including branching networks of choroidal vessels, polypoidal lesions, severe degeneration of the elastic laminae, and tunica media of choroidal vessels [109]. Similar to the role of HTRA1 in arthritic disease, which contributes to the destruction of extracellular matrix [110], upregulation of HTRA1 in RPE seems to degrade elastic lamina of Bruch's membrane, which will exhibit RPE atrophy and photoreceptor degeneration, as well as development of choroidal neovascularization in senescent mice [109].

Compared to *HTRA1*, the role of *ARMS2* in AMD pathology remains to be clarified. *ARMS2* seems to be associated with a particular visual function of primates, as the conserved ortholog of *ARMS2* is observed in chimpanzee, but not in other vertebrates [56]. The subcellular distribution of ARMS2 protein is controversial, because its expression has been shown in the mitochondrial outer membrane of photoreceptors [56], or in the cytosol [111]. Besides *ARMS2* A69S variant, an indel polymorphism of *ARMS2* has been shown in the 3′-untranslated region (UTR) and flanking region [112]. The association of this indel with AMD is almost the same as that of *ARMS2* A69S and *HTRA1* rs11200638, as these variants are in strong LD. The *ARMS2* indel variant is highly unstable at the mRNA level, consequently resulting in the absence of protein expression [112]. Recent study, however, a premature stop variant in *ARMS2* (R38X, rs2736911), not the indel variant, seems to be associated with the decrease in stability of *ARMS2* transcript [106]. Nevertheless, both R38X and indel variants are less likely to play a pathogenic role in AMD. Although strong associations of *ARMS2* variants with AMD susceptibility have been established by human genetics, it remains to be defined whether mRNA turnover and protein stability of *ARMS2* directly contribute to the pathogenesis of this disease.

Recent advance in cell reprogramming technology enables us to provide a good model for early stage AMD patient-specific cells by generating induced pluripotent stem cell (iPSC)-derived RPE from patients [113]. An unbiased proteome screen of patient-specific iPSC-derived RPE cell lines that were treated with A2E revealed that superoxide dismutase 2 (SOD2) is a downstream target of *ARMS2/HTRA1* and mediates antioxidative defense in the genetic allele's susceptibility of AMD.

It was also shown that the combination of risk markers may have clinical relevance as additive accumulation of risk from effect alleles at *CFH* and *ARMS2/HTRA1* loci in both Caucasian and Asian populations [63,114,115]. Commercial genome-wide scans have been paid attention for the risk prediction of AMD based on *CFH*, *C2/BF*, and *ARMS2* loci. Health-related direct-to-consumer genetic testing in the United States, however, has been recently halted by the US Food and Drug Administration in 2013 due to the reason that such testing is "unapproved and uncleared device" without showing analytical and clinical validity [116].

Similar to wet AMD, choroidal neovascularization is also occurred in highly myopic eyes due to the excessive axial elongation of the eye, leading to the rupture of Bruch's membrans and the atrophy of choriocapillaris [117]. In a Japanese cohort of highly myopic patients aged over 50 years, *ARMS2* A69S, *HTRA1* rs11200638, and *CFH* Y402H variants seem to have no significant association with the phenotype of choroidal neovascularization [118]. Although there might be some similarities between AMD-derived and highly myopia-derived neovascularization, genetic factors involved in these diseases will be distinctly different. GWAS in a Japanese cohort revealed that *Zic family member 2* (*ZIC2*) and *Ras protein-specific guanine nucleotide-releasing factor 1* (*RASGRF1*) are susceptibility genes for high myopia [119], which have been never shown in the context of AMD susceptibility.

3.3. Other AMD susceptibility genes

GWAS of large samples by Caucasians and Japanese have revealed additional susceptibility loci for advanced AMD: the Tufts/Massachusetts General Hospital (MGH) study included 979 cases and 1,709 controls on the Affyetrix 6.0 platform [120], the Michigan, Mayo, AREDS, Pennsylvania (MMAP) AMD case–control study included 821 cases and 1,709 controls on the Illumina Human370 Bead Chips platform [121], and the Japanese collaborative study included 827 cases on the Illumina Human610-Quad BeadChip platform and 3,323 controls on the Illumina HumanHap550v3 BeadChip platform [122]. The Tufts/MGH study revealed the association between AMD and a variant in the *hepatic lipase*

gene (LIPC) on chromosome 15q21-q23, which controls an enzyme involved in HDL cholesterol metabolism [120]. The study showed a direct cause and effect relationship between HDL levels and incidence of AMD for the first time. The MMAP study identified a susceptibility locus on chromosome 22q12 near *TIMP3*, an inhibitor for metalloproteinases that involved in degradation of the extracellular matrix, and previously identified as a responsible gene for Sorsby fundus dystrophy [123,124] and implicated in aging and early-onset maculopathy [125]. The data also revealed strong association signals with alleles at the loci of *LIPC* and *cholesteryl ester transfer protein in plasma (CETP)* on 16q21 loci, which were previously associated with high-density lipoprotein cholesterol (HDL-c) levels in blood [121]. In regard to exudative AMD susceptibility in Japanese, GWAS was performed for 827 cases on the Illumina Human610-Quad BeadChip and 3,323 controls on the Illumina HumanHap550v3 BeadChip, and identified 2 susceptibility loci: *TNFRSF10A-LOC389641* on chromosome 8p21 (rs13278062) and *REST-C4orf14-POLR2B-IGFBP7* on chromosome 4q12 (rs1713985) [122].

Collaborative meta-analyses across the world (included >17,100 cases and >60,000 controls) have further uncovered common risk variants for advanced AMD in 19 susceptibility loci [126]. Previously established susceptibility loci were validated in this study, including *ARMS2-HTRA1*, *CFH*, *C2-CFB*, *C3*, *TIMP3*, *APOE*, *CETP*, *VEGFA*, *LIPC*, *CFI*, *COL10A1*, and *TNFRSF10A*. Seven additional susceptibility loci were identified for the first time: *COL8A1-FILIP1L* (rs13081855), *IER3-DDR1* (rs3130783), *SLC16A8* (rs8135665), *TGFBR1* (rs334353), *RAD51B* (rs8017304), *ADAMTS9* (rs6795735), and *B3GALTL* (rs9542236) (Table 1) [126]. Based on the findings by the world-wide collaborative meta-analyses, the evaluation of the independent impact of new genetic variants on the progression of AMD was performed by controlling for established risk factors including 6 established loci in 5 genes (e.g., *CFH*, *ARMS2/HTRA1*, *C2*, *CFB*, and *C3*), and demographic, behavioral, and macular characteristics [127]. According to this study, rare variant *CFH* R1210C and common variants in *COL8A1* and *RAD51B* will contribute to the progression to advanced AMD, controlling for all known AMD genetic loci. Moreover, borderline associations of progression to advanced AMD with *VEGFA*, *COL10A1*, and *TIPM3* were shown, but not with *LIPC*, *ABCA1*, *TNFRSF10A*, *APOC1|APOE*, *DDR1*, *SLC16A8*, *TGFBR1*, and *ADAMTS9* [127]. In regard to the functions of new AMD susceptibility genes, the *COL8A1* gene encodes one of the two alpha chains of type VIII collagen, which is a member of the short-chain nonfibrillar collagen family. Type VIII collagen is present in small amounts in normal arteries; however, synthesis is dramatically increased after injury and during development of atherosclerosis in experimental animals and humans [128]. In the eye, it is a major component of the multiple basement membranes, including Bruch's membrane and the choroidal stroma [129]. The protein encoded by *RAD51B* is a member of the RAD51 protein family, and is essential for DNA repair mechanisms. This gene is also involved in cell cycle delay and apoptosis [130].

As abovementioned, AMD prevalence, frequencies for genetic risk alleles and AMD phenotypes differ among ethnic populations. The prevalence of early AMD has been reported 5.4% in whites, 4.6% in Chinese Americans (predominantly born outside the U.S.), 2.4% in blacks, and 4.2% in Hispanics based on the Multi-Ethnic Study of Atherosclerosis (MESA) [131], a 10-year longitudinal study supported by the National Heart, Lung, and Blood Institute with the goals of identifying risk factors for subclinical atherosclerosis, for quantitative progression of subclinical atherosclerosis, and for transition from subclinical disease to clinically apparent events [132]. Estimated prevalences of late AMD were 0.6% in whites, 1.0% in Chinese Americans, 0.3% in blacks, and 0.2% in Hispanics. In the 2005–2008 National Health and Nutritional Examination Survey (NHANES), the prevalence of any AMD lesion was similar as 7.3% in whites, 5.1% in Maxican Americans, and 2.4% in blacks [133]. The racial differences in AMD prevalence may not be explained even after controlling for known non-genetic risk factors including body mass index, smoking, alcohol drinking history, diabetes, and hypertension status. It is also notable that the frequency of exudative AMD was highest in Chinese with age- and gender-adjusted odds ratio as 4.3 compared with whites [131]. One possible reason for higher prevalence of exudative AMD for Chinese may be due to a higher prevalence of PCV, which situation is similar to that in Japanese. Genetic analysis of MESA data also revealed that whites, blacks, and Hispanics with the *CFH* Y402H CC homozygous genotype had the highest frequencies of early AMD compared to those with the *CFH* Y402H TT wild genotype but did not explain the higher early AMD in non-Hispanic whites compared to blacks [134]. The strong relationship of the *ARMS2* variant genotype to AMD in Chinese Americans in the MESA and the infrequency of *CFH* Y402H CC variant observed in the MESA are consistent with other studies of Asians including Japanese. [115,126,135–137]. Similar to *CFH* Y402H variant, the nonsynonymous *C3* variant rs2230199 is common in Europeans but rare in Asians and Africans [126,137]. In summary, *ARMS2/HTRA1* risk variant is likely to be associated with exudative AMD that is more common in Asians compared with Caucasians, whereas variants of *CFH* and its related complement genes seem to be well associated with dry AMD and geographic atrophy that are more common in Caucasians than in Asians [4]. Nevertheless, differences in the prevalence of neovascular and atrophic forms of AMD between Asians and Caucasians still remain to be elucidated as the differences are much larger than can be expected by the frequency differences of *ARMS2/HTRA1* and *CFH* risk variants alone.

3.4. Variants associated with therapeutic efficiency

In terms of neovascular AMD, VEGF is a key regulator for choroidal neovascularization [138]. In contrast, a secretary protein pigment epithelium-derived factor (PEDF), or SERPINF1, is a potent anti-angiogenic agent that inhibits the migration of endothelial cells [139]. An imbalance between VEGF and PEDF will contribute to the development of choroidal neovascularization in AMD [140,141]. Therefore, the application of anti-VEGF therapy has remarkably improved functional outcomes for patients affected by wet AMD, reducing the incidence of blindness in the elder people [142]. In a Japanese population, *VEGF* rs699947 polymorphism in its promoter region on chromosome 6p21 is significantly associated with visual outcomes after anti-VEGF therapy, intravitreal treatment with bevacizumab [143]. Nonsynonymous variant of *PEDF* rs1136287 (The72Met) on chromosome 17p13, can be also associated with visual outcomes after intravitreal bevacizumab treatment [143]. Recently, an inhibitor for mammalian target of rapamycin (mTOR), temsirolimus, has been shown to inhibit the proliferation and migration of RPE and endothelial cells, and decreases VEGF and PDGF expression [144]. Besides anti-VEGF therapy, the mTOR inhibitor can be a potential new drug for AMD. Variants for VEGF and PEDF may also be relevant for the prediction of the prognosis by the potential treatment with mTOR inhibitor.

Verteporfin photodynamic therapy (PDT) is another efficient treatment for AMD. *CFH* Y402H variant has been reported to be associated with responses to PDT in a Caucasian population in the United Kingdom [145]. In another Caucasian cohort in the United States, *CFH* Y402H variant, but not *ARMS2/LOC387715* A69S variant, significantly associated with visual outcomes by PDT [146] as well as by anti-VEGF therapy [147]. There might be ethnic variability in regard to therapeutic responses, as *HTRA1* rs11200638 variant has been shown to be significantly associated with visual

outcomes of AMD patients by PDT in a Japanese cohort [148]. *CFH* rs1410996 and *rs2274700* variants are also mildly associated with outcomes by PDT in this population [148].

Considering no effective therapies for advanced geographic atrophy is available compared with tAMD, RPE transplantation will be a potential new treatment for the disease. In this context, RIKEN Center for Developmental Biology in Japan, has recently started a pilot study to assess the safety and feasibility of the transplantation of autologous induced pluripotent stem cell (iPSC)-derived RPE cell sheets in patients with exudative age-related macular degeneration [149]. A new method for integration-free iPSC generation has been established using Sendai virus vector nowadays, thus it will be beneficial for clinical application by avoiding tumorigenetic activity of iPSCs [150]. Dr. Takahashi and her colleagues generated human iPSC-derived RPE (hiPSC-RPE) cell sheets optimized to meet clinical use requirements, including quality, quantity, consistency, and safety. The hiPSC-RPE cell sheets are generated as a monolayer of cells with expressing RPE markers, forming tight junctions, and showing phagocytotic ability and gene-expression patterns similar to those of native RPE [151].

4. Animal models for human AMD

In regard to gene-targeting models for AMD that will reveal an involvement of macrophages in the pathogenesis, aging mice deficient either monocyte chemotactic protein-1 (MCP-1), a chemoattractant for macrophages and memory T cells, or its cognate ligand chemokine C–C receptor-2 (CCR-2) [152] are shown to develop retinal degeneration with typical features of both dry and wet AMD [153]. The pathology of these mice eyes exhibits various symptoms of AMD: the accumulation of lipofuscin and drusen beneath RPE cells, photoreceptor atrophy, and choroidal neovascularization [153]. MCP-1 is known for its proinflammatory role as well as immunomodulatory role. Cells of the blood retinal barrier, including RPE layer, constitutively produce MCP-1 and can secrete high levels of the molecule after exposure to other cytokines and chemokines [154]. The accumulation of complement components, complement regulatory proteins and IgG in these *MCP-1* or *CCR-2* knockout mice suggests that impaired macrophage recruitment allows accretion of proteins associated with complement activation and immune complex deposition. Impaired macrophage mobilization *in vivo* prevents clearance of complement-related proteins and IgG, as these cells are known to scavenge immune complexes through complement opsonization *in vivo* [153].

In senescent mice deficient neprilysin, a critical metallopeptidase for amyloid beta catabolism, amyloid beta has been detected both within RPE cells as well as subepithelial deposits, putatively leading to RPE degeneration with vacuoles and imbalance of cytokines [155]. Amyloid beta will also upregulate MCP-1, which will recruit macrophages and microglia into the subretinal space, and recruited cells will be activated by amyloid beta to produce various cytokines including TNF-α and IL-1β. The elevation of cytokines will subsequently activate complement pathway, such as upregulation of factor B [156].

A model of mice deficient in Cu, Zn-superoxide dismutase (SOD1) is also useful for studying the pathology of human AMD [157]. Senescent *Sod1* knockout mice exhibited an age-dependent phonotype with drusen, thickened Bruch's membrane, and choroidal neovascularization. RPE cells of *Sod1* knockout mice seem to be affected by oxidative damage, and their junctional integrities were damaged with the disruption of beta-catenin-mediated cell adhesions. The mice model provides an insight to the effects of oxidative stress to the dysregulation of blood retinal barrier including RPE cell layer and Bruch's membrane, leading to the onset of choroidal neovascularization.

The contribution of oxidative damage to AMD will be also explained by a model of mice deficient nuclear factor erythroid 2-related factor 2 (NRF2), a transcription factor that plays key roles in antioxidant and detoxification responses. The mice exhibit a phenotype wit drusen-like deposits, accumulation of lipofuscin, spontaneous choroidal neovascularization and sub-RPE deposition of inflammatory proteins after 12 months [158]. Notably, accumulation of autophagy-related vacuoles and multivesicular bodies was observed within the RPE and in Bruch's membrane of the aged mice, suggesting that the disorder of autophagy will link oxidative damage to inflammatory processes.

The dysregulation of cellular clearance will play a particular role in the pathogenesis of dry AMD. Mice deficient aryl hydrocarbon receptor (AhR), a nuclear receptor that regulates xenobiotic metabolism and detoxification, exhibit decreased visual function and develop dry AMD-like pathology, including disrupted RPE cell tight junctions, accumulation of RPE cell lipofuscin, basal laminar and linear-like deposit material, Bruch's membrane thickening, and progressive RPE and choroidal atrophy [159]. The absence of AhR may stimulate collagen secretion from RPE cells together with oxidized low-density lipoprotein, promoting extracellular accumulation within deposits, Bruch's membrane, and choroid.

Cfh-deficient mice have been originally known as a model for membranoproliferative glomerulonephritis, which could be occurred by uncontrolled activation of C3 in the glomerulus [160]. Two-year-old *Cfh* -deficient mice have a phenotype with an increase in autofluorescent subretinal deposits, an accumulation of complement C3 in the neural retina, and reduced rod response amplitudes on electroretinography [161]. Because young *Cfh* -deficient mice exhibited no significant changes in retina other than a modest thickening, aging will be an important factor in the pathology of Cfh dysregulation [162].

Overall, the gene-manipulated animal models for human AMD will provide a better insight to the mechanisms underlying AMD pathogenesis, as well as will be applied to the validation and development of alternative treatments for the advanced disease.

5. Non-genetic factors contribute to AMD pathogenesis

Like other common diseases, both genetic and non-genetic factors are involved in the etiology of AMD. Genetic factors may contribute to 50% or more percentage of AMD risk, yet several non-genetic factors may also play important roles for the development and progression the disease. It might be assumed that the interventions trying to minimize the role of non-genetic factors will reduce the incidence of AMD and/or the progression to advanced stages.

Among non-genetic factors, aging and smoking are considered as leading causes of the disease. The impact of smoking on AMD etiology has been described by several groups [163–165]. Before the genetic factors for AMD have been identified, the association of AMD and cigarette smoking was established by several cohort studies for both Caucasians and Asians [166–176]. Former smoking habit seems to be a risk factor for AMD after cessation of smoking [175], although quitting smoking will be beneficial to reduce the risk of AMD [177–179]. Some studies showed that male smokers are more susceptible to AMD than female smokers [167], although the finding is controversial [170]. In Caucasians, it has been known that there is no association of sex with AMD risk, although male AMD patients are predominant in Japanese. In Nagahama study in Japan, smoking was significantly associated with both early and late AMD stages and retinal pigment abnormalities, but not with drusen. The prevalence of retinal pigment abnormalities was significantly higher in men [180]. Cigarette smoking is also an environmental risk factor for PCV [181]. Although several lines

of evidence show the adverse effect of smoking on AMD pathogenesis, it is not clear how cigarette and which component(s) exerts damage on the central region of chorio-retinal tissues. Experimental studies may provide some information in regard to this issue. Benzo(a)pyrene, a toxic element in cigarette smoke, for example, will damage mitochondrial DNA of cultured RPE cells, increase lysosomal and exocytotic activities, and activate complement pathway components [182]. Endoplasmic reticulum (ER) stress and lipid dysregulation can be occurred in mice by long-term smoke inhalation [183]. Cigarette smoke extract can trigger the activation of alternative complement pathway in cultured RPE cells, resulting in oxidative stress and lipid deposition [183]. Based on these findings, adverse smoking effect on AMD might be managed by anti-complement therapies.

The reduction of antioxidants in the central retina will be a risk factor for AMD. In regard to the effects of nutrients to AMD etiology, NIH's National Eye Institute led The Age-Related Eye Disease Study (AREDS), a multi-center randomized trial designed to assess the effects of oral supplementation of high dose of vitamins C and E, beta-carotene, and the minerals zinc and copper (AREDS formulation) for the treatment of AMD and cataract. In the first AREDS trial, participants with AMD who took the AREDS formulation were 25% less likely to progress to advanced AMD over the five-year study period, compared with participants who took a placebo [184]. The complication of the first AREDS trial is that there was an association between β-carotene and risk of lung cancer among former smokers. There have been also concerned that the high zinc dose in AREDS could cause minor side effects such as stomach upset.

In subsequent AREDS2 launched in 2006, the effects of high supplemental doses of the dietary xanthophylls (lutein and zeaxanthin) and omega-3 long-chain polyunsaturated fatty acids (LCPUFAs) including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) that abundantly involved in fish oil, as well as the effects of eliminating β-carotene and reducing zinc in the original AREDS formulation on the development and progression of AMD have been evaluated [185]. Lutein and zeaxanthin are the most common xanthophylls in green leafy vegetables such as spinach and broccoli, as well as in egg yolks [186]. They have ability to act as scavengers for reactive oxygen species [187], which will be increasingly produced by oxidative stress and aging. The macular carotenoids include dietary lutein/zeaxanthin and the metabolite *meso*-zeaxanthin abundantly [188], those pigments will contribute to the formation of yellow spot in the central retina [189,190]. The effect of the macular carotenoids on blue-light filtration and color perception has been well established [190]. Previous studies revealed that a higher dietary intake of carotenoids, specifically lutein and zeaxanthin, were associated with reduced AMD risk [191]. In regard to DHA/EPA, evidence has been revealed that the consumption of fish with abundant involvement of omega-3 LCPUFAs reduces AMD risk in the U.S. Twin Study of AMD [192].

The AREDS2 trial revealed, however, that the addition of lutein/zeaxanthin, DHA+EPA, or both to the AREDS formulation in primary analyses did not further reduce risk of progression to advanced AMD [185]. Even though, the study recommends that lutein/zeaxanthin could be an appropriate carotenoid substitute in the AREDS formulation because of potential increased incidence of lung cancer in former smokers. In terms of the evaluation the treatment effect of lutein/zeaxanthin on the 2 forms of late AMD, there seems a trend toward a reduction particularly in the rates of development of neovascular AMD compared to geographic atrophy, although the development rates of latter form were rather low in AREDS2 and there was a limitation for precise evaluation [193]. This finding is similar to that in AREDS, as the long-term assessment of the beneficial effects of the AREDS formulation was most prominent in preventing the development of neovascular AMD [194]. The totality of evidence on the beneficial and adverse effects from AREDS2 and other studies suggest that lutein/zeaxanthin could be more appropriate than β-carotene for the new AREDS2 formulation.

AMD and cardiovascular disease (CVD) may share similar risk factors including such as aging, smoking, dietary fat, and hypercholesterolemia [195]. A systematic review and meta-analysis of population-based cohort studies suggest that early AMD was associated with a future risk of CVD events, including coronary heart disease and stroke [196]. C-reactive protein (CRP) is an inflammatory marker known for the association with cardiovascular disease. A meta-analysis showed that high serum/plasma CRP levels substantially associate with incidence of late AMD [197]. CRP molecule has shown to have a strong binding affinity to the CFH protein, which affinity will be modulated by Y402H polymorphism that is predominant in Caucasian AMD patients [198]. Factor H purified from sera of AMD patients with a homozygous genotype of 402His variant showed a reduced binding to CRP compared with that from sera of controls homozygous for 402Tyr variant. Thus, the reduced binding of 402H variant to CRP may lead to an impaired targeting of factor H to cellular debris, a reduction in debris clearance, and enhanced inflammation in the chorio-retinal interface.

High fat diet can be also involved in the development of AMD. Considering AMD as one of the symptoms for metabolic syndrome, dietary effects will contribute to the pathogenesis of the disease. In observations from the Beaver Dam Eye Study, it has been shown that female nonsmokers have risk of late AMD associated with increasing measures of greater obesity and increased risk of early AMD associated with greater body mass index (BMI) [199]. Since genes involved in cholesterol metabolism, including *LIPC*, *CETP*, *LPL*, *ABCA1*, and *APOE*, have been identified as AMD susceptibility genes, higher serum level of cholesterol due to high fat diet and genetic background will contribute to the pathogenesis of AMD.

Sunlight or blue light exposure is known as another risk factor for AMD. A recent meta-analysis to investigate the relationship between sunlight exposure and AMD shows that a pooled odds ratio was 1.379 (95% confidential interval 1.091–1.745) [200]. Epidemiological evidence needs to be accumulated to reveal the distinct effect of sunlight exposure on AMD pathology, yet experimental findings seem to be sufficient to explain this point. A mice study showed that light exposure induced reactive oxygen species and activated Rho/Rho-associated coiled–coiled forming kinase pathway, resulting in the disruption of cell–cell junctions and the destruction of RPE-dependent barrier structure [201]. In *Abca4*$^{-/-}$ *Rdh8*$^{-/-}$ mice, which have many features associated with human Stargardt disease and AMD, brief exposure of the retina to bright light results in acute retinal degeneration, including retinoid-dependent formation of fluorescent metabolic by-products (e.g., A2E) within rod photoreceptor cells and a remarkable expansion/swelling of rod outer segments, followed by secondary infiltration of microglia/macrophages [202].

6. Conclusions

Recent high-throughput analysing technologies including GWAS and next-generation sequencing have identified genetic factors that are strongly or marginally associated with the susceptibility of AMD. Non-genetic factors such as smoking, diet, and light exposure will also modify the pathogenesis of AMD. *ARMS2/HTRA1* and *CFH* have been determined as major vulnerable genes for AMD, the former is more susceptible for neovascular AMD and the latter is more associated with atrophic AMD. Neovascular AMD is more common in Asians than in Caucasians whereas geographic atrophy is more common in Caucasians vice versa, which mechanisms

remain to be elucidated. Anti-VEGF therapy is a standard treatment for neovascular AMD, whereas another therapeutic agents remain to be developed for the management of atrophic AMD. Phenotype-specific and ethnic-specific genetic analysis for AMD will provide insights into the pathophysiology of AMD. Animal models that mimic phenotypes of clinical AMD will also be useful for the better understanding of molecular mechanisms underlying the disease and the screening of potential therapeutic agents. Although AMD lesion usually begins as a tiny pinhead placed into the macula, it could turn out to be a catastrophe for central vision in advanced stages. Thus, genetic and epidemiologic studies for AMD will contribute to the prevention of central vision loss and the maintenance of quality of vision to achieve productive aging.

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