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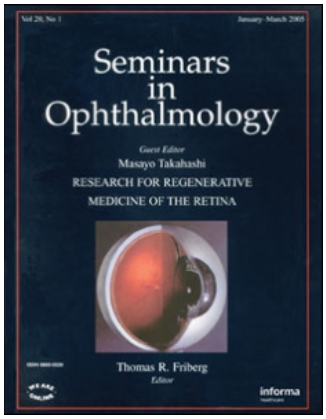

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Review of Genetics in Age Related Macular Degeneration

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Review of Genetics in Age Related Macular Degeneration

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ABSTRACT Age-related macular degeneration (AMD) is a degenerative disease of the retina and the leading cause of blindness in industrialized countries. AMD is a complex disease caused by the combination of genetic predisposition and environmental factors. The prevalence of AMD increases with age. The adverse effect of smoking is well established. Genetic predisposition has been demonstrated by familial aggregation studies and twin studies. Using genome linkage scan and association studies, multiple potentially causative genes have been identified. The chromosomes most commonly implicated are 1q25-31 and 10q26. In particular, variants in the gene for the complement factor H (CFH) and the genes PLEKHA1/LOC387715/HTRA1, Factor B (BF) and complement component 2 (C2) have been implicated as major risk or protective factors for the development of AMD. There have been some advances in the treatment of this condition; however, a complete cure remains remote but hopeful. Understanding the causative environmental and genetic interactions will facilitate the development of future preventive methods and treatments.

KEYWORDS age-related macular degeneration (AMD), apolipoprotein E (APOE), adenosine triphosphate (ATP), binding cassette rim (ABCR) protein, complement component 2 (C2), Factor B (BF), Complement Factor H (CFH) gene, choroidal neovascularization (CNV), geographic atrophy (GA), Clinical Age-Related Maculopathy Grading System (CARMS), LOC387715/HTRA1 gene, retinal pigment epithelium (RPE), single nucleotide polymorphism (SNP), vascular endothelial growth factor (VEGF)

CLASSIFICATION

AMD is a degenerative disorder of the retina in persons equal to or older than 50 years of age with the following abnormalities in the macula: soft drusen equal to or greater than 125 microns, hyperpigmentation and/or hypopigmentation of the retinal pigment epithelium (RPE), RPE detachment, subretinal hemorrhages, geographic atrophy of the RPE, or choroidal neovascularization and subretinal fibrous scarring.

AMD can be divided into early and late forms. Early AMD is characterized by the presence of drusen and RPE pigmentary abnormalities. Late AMD includes two clinical forms: (1) an atrophic/dry form, which is identified by geographic atrophy of the RPE; and (2) a neovascular/wet/exudative form, which is characterized by proliferation of abnormal choroidal vessels, which penetrate

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the Bruch's membrane and RPE layer into the subretinal space, forming extensive clots and/or scars.[1,2] The Clinical Age-Related Maculopathy Grading System (CARMS) classifies AMD into early, intermediate and late stages. Late stages are separated into either geographic atrophy involving both central and non-central areas of the macula or neovascular disease.[3]

PREVALENCE

It is estimated that 1.75 million people in the US have AMD. The prevalence of neovascular AMD and/or geographic atrophy in the US population 40 years and older is 1.47%.[4] The prevalence of AMD varies significantly in different locations and racial/ethnic groups around the world. AMD is more prevalent among whites than blacks, especially the more severe forms of AMD.[5–10] African-Americans with AMD have more peripapillary choroidal neovascularization than whites.[11]

Neovascular AMD was more prevalent in the U.S. Beaver Dam and Australian Blue Mountain populations than in the European city of Rotterdam, Netherlands.[12,13] Geographic atrophy was more frequent in Chinese, Icelandic and Norwegian populations compared to other groups.[14–17] Among Hispanic and non-Hispanic whites living in the U.S., there is also a significant difference. Late-stage AMD was significantly less frequent in Hispanics vs. non-Hispanics. Also, non-Hispanic whites living in Beaver Dam, Wisconsin, have higher prevalence of AMD than those living in the San Luis Valley of southern Colorado.[18]

RISK FACTORS FOR AMD

The most consistent major risk factor for AMD is age. AMD is least common before 55 years of age and most common in persons 75 years of age or older.[6,12,19–22] Approximately 30% of people 70 years old or older have some signs of maculopathy, and of these, 6–8% have advanced stages of AMD. It is also estimated that more than 15% of white women older than 80 years have neovascular AMD and/or geographic atrophy.[4]

The relationship between smoking and AMD is well known.[12,20,23–30] Smoking is associated with a twofold-increased risk of developing AMD.[23,24,27,30,31] Exposure to sunlight has also been associated with the development of early AMD;[32] however, this association could not be demonstrated in some studies, even with high levels of sunlight exposure.[33–35] Other possible risk factors include hypertension,[30,36,37] raised plasma fibrinogen levels,[38] elevated C-reactive protein levels,[39] and increased body mass index (BMI).[40,41] In a Chinese population, hyperopic refractive error was the single most important risk factor for AMD other than age. Other associated risk factors in this study included living in a rural region and lower level of education.[42]

Conflicting results have been found with iris color and gender. Light iris color was reported to be a risk factor in some studies,[9,43,44] but inconsistently related in others.[45,46] Regarding risk associated with gender, one Japanese study found AMD to be more prevalent among males,[36] while others among females.[30] Heavy alcohol consumption, particularly beer, has been associated with an increased risk of having AMD,[29,47] while moderate wine consumption may have a protective effect,[48] although confounding factors like smoking and diet were not accounted for in all studies. No association was found between AMD and low to moderate intake of alcohol in a large prospective study controlling for other factors.[49]

Several studies have identified certain dietary behaviors as increasing or decreasing risk of AMD. High intake of fat has been associated with increased risk of AMD.[50–52] Antioxidants such as carotenoids (mainly dark green and leafy vegetables), zinc or vitamins C and E have been associated with a reduced risk for AMD.[53–56] Fruit, nut, fish and omega-3 fatty acid consumption are also suggested protective factors for AMD.[52,57–59]

PATHOGENIC THEORIES FOR AMD

Zarbin et al. described a sequence of events associated with patients' susceptibility to AMD. Aging and oxidative stress leads to RPE and choriocapillaris injury. This injury can cause a chronic inflammatory response within Bruch's membrane and the choroid and lead to formation of an abnormal extracellular matrix (ECM). The abnormal ECM alters the diffusion of nutrients to the retina, leading to choroidal neovascularization and/or atrophy of the retina, RPE, and choriocapillaris. In this explanation, both the environment and multiple genes can alter a patient's susceptibility to AMD.[60]

The Turnover of the Photoreceptor Outer Segment and the Formation of Lipofuscin

In the retina there is a continuous turnover of the photoreceptor outer segments. Material discarded from

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the outer segments is metabolized by the RPE and cleared by the choriocapillaris. Accumulation of debris from the RPE released into Bruch's membrane contributes to the formation of drusen. This membrane thickens with age.[61]

The outer segment discs form as invaginations at the base of the cells and they move to the tip of the outer segment. The RPE phagocytizes the outer segment tips daily. The turnover rate of the outer segment is about 10 days in humans. Until around 30 years of age, the RPE digests the phagocytized outer segment material, but afterward an indigestible lipofuscin product starts to accumulate. Peroxidation of lipofuscin in the lysosomal system is influenced by high oxygen concentrations and blue light, which create reactive oxygen species that damage the lysosomal membrane. Further release of lytic enzymes and reactive oxygen damages the RPE cells, contributing to the formation of drusen.[61]

One experiment that used cultured RPE cells fed with photoreceptor outer segments at two different oxygen concentrations found that cells kept in 40% oxygen accumulated two times more lipofuscin in 3 weeks than those kept at 8%.[62] This experiment demonstrates that oxidative reactions are implicated in lipofuscin formation. In another experiment, antioxidants used in the culture medium (vitamin E, zeaxanthin and lutein) reduced lipofuscin formation significantly ($p < 0.01$); vitamin E was the most effective and lutein the least effective.[63,64] The Age-Related Eye Disease Study (AREDS) supported these basic experimental findings. This study showed that high doses of antioxidants and zinc reduced the risk of advanced AMD by 25% over five years.[65]

The Free Radical Theory of Aging

Oxidative stress has been associated with the pathogenesis of neurodegenerative diseases. Basic research demonstrated that mice deficient in Cu, Zn-superoxide dismutase have retinal features similar to human AMD. Drusen, thickened Bruch's membrane, and CNV were observed in older mice. The number of drusen increased with age. Exposure of young mice to excess light also induced drusen formation. The RPE showed oxidative damage and disruption of the β-catenin mediated cellular integrity (a key molecule responsible for the integrity of the RPE). These findings suggest that oxidative stress may affect the proteins necessary for the integrity of the RPE cell layer.[60,66]

The Immune Theory and Inflammation

Patel et al. found evidence that the immune system participates in the pathogenesis of AMD. They analyzed the sera of patients with AMD using indirect immunohistochemistry and Western blot analysis. A statistically significantly ($p = 0.02$) higher titer of circulating anti-retinal antibodies in comparison with controls was found. This suggests a role for the immune system in the development of AMD.[67]

Inflammatory responses have been associated with drusen formation. Drusen contain proteins like vitronectin, complement, and immunoglobulins that modulate the retinal response to inflammation.[68–70] Inflammatory cells, including macrophages, multinucleated giant cells, fibroblasts, mast cells, and dendritic cells, which are potent antigen-presenting cells, have been also associated with the prevalence of drusen.[60,71–74]

A combined hypothesis is that immune responses and associated genetic polymorphisms modulate susceptibility to AMD. This could explain the roles of inflammation and genetic predisposition in the pathogenesis of AMD. Genes that encode human leukocyte antigen (HLA), Factor B (FB), complement component 2 (C2) and complement factor H (CFH) are of particular interest and are consistent with this hypothesis.[75–80]

Genetic Predisposition

Twin Studies

The concordance for AMD in monozygotic twins has been demonstrated in several small case series.[81–84] Klein et al. reported eight of nine monozygotic twins were concordant for AMD.[81] Meyers et al. reported 100% concordance in 25 monozygotic twins compared to 42% concordance in 12 dizygotic twins,[82] and Gottfredsdottir et al. found 90% concordance in 50 monozygotic twins.[83] In a large population-based twin study of 840 WWII veterans in the US, Seddon et al. quantified the roles of environment and heredity by studying both monozygotic and dyzygotic twins and their AMD concordance rates using complex twin analyses. Genetic factors explained 46% to 71% of the variation in the overall severity of the disease, whereas unique environmental exposures accounted for 19% to 37% of the variance.[84]

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Familial Aggregation Studies

The genetic predisposition for AMD has been investigated by comparing AMD rates in relatives of cases vs AMD rates in relatives of controls. Seddon et al. found that the prevalence of AMD among first-degree relatives of cases, especially those with the exudative form, was greater than among first-degree relatives of controls (23.7% vs 11.6%).[85] When comparing cases with controls, Hyman et al. found that cases were more likely to report a family history.[86] In a case-control study from Northern Ireland, 20/81 (25%) siblings of patients with AMD were affected but only 1/78 (1%) siblings of controls had the disease, giving a relative risk of 19.[87] Klaver et al. studied fundus photographs of first-degree relatives of 87 cases with late AMD and compared them with 135 first-degree relatives of controls. The odds ratio for early AMD for siblings of cases vs. controls was 4.8 and for offspring of cases vs. controls was 6.6.[88] A population-based study conducted from 1988-1990 in Beaver Dam, Wisconsin, found that AMD in older siblings predicts the development of AMD in younger siblings, also suggesting a strong family predisposition for AMD.[89]

GENE IDENTIFICATION

Linkage Studies

Genetic linkage is the phenomenon in which alleles at loci close together on the same chromosome are inherited jointly, because it would be rare for a crossover to occur between the loci at meiosis. In linkage studies, two genes are considered. One is the gene for the disease trait (unknown locus) and the other is a marker trait (known locus). The more frequently that these two genes appear together in pedigrees, the more possible it is that they are in close proximity in the chromosome.

Using linkage analysis, genomic regions of several AMD susceptibility loci have been identified. The ARMD1 gene locus at 1q31 was the first linkage region identified in a large family with a predominantly dry AMD phenotype.[90] Additional genome-wide scans of multiplex AMD families have also found linkage to this region.[91–94] Further analysis of the ARMD1 region identified the Gln5345Arg allelic variant in exon 104 of the fibulin-6 gene, in some individuals with AMD.[95] This gene, also known as hemicentin-1, encodes laminins, a class of ECM proteins present in the basal lamina of the RPE, Bruch's membrane, and choriocapillaris. However, independent groups did not support the association of the Gln5345Arg variant in hemicentin-1 with AMD.[92,96] Mutations of other fibulin genes have also been associated with AMD.[97,98]

Evidence of linkage has also been found in regions at chromosomes 1q, 2p, 3p, 4q, 10q, 12q and 16q as well as several other chromosomes in different populations.[91–93,99]

A meta-analysis of genome-wide linkage studies in AMD has confirmed these candidate regions. In that study, the strongest evidence for an AMD susceptibility locus was found on chromosome 10q26, and the second most significant region identified was on chromosome 1q, which contains the CFH gene.[100] In another linkage analysis, followed by family-based and case-control association analysis, a coding change (Ala69Ser) in the LOC387715 gene on chromosome 10 was identified as the second major AMD-susceptibility allele.[101,102]

Association Studies

Association studies assess if specific alleles happen at higher frequency than explained by chance in a population of diseased subjects compared with healthy controls. Genes found in diseases similar to AMD have been investigated. If there is evidence of such association, it might indicate that the allele of interest is a disease-causing allele or that it is in linkage disequilibrium with a disease causing allele. Linkage disequilibrium refers to the occurrence of certain combinations of linked alleles in greater proportion than expected from the allele frequencies at the loci.[103]

IMPORTANT GENES IMPLICATED IN AMD

Chromosome 1p: Adenosine Triphosphate (ATP) Binding Cassette Rim (ABCR) Protein

The ABCR gene is implicated in Stargardt disease (STGD), the most common form of hereditary recessive macular dystrophy. Mutations of this gene have also been reported in patients with AMD.[104–107] The exudative form is rarely associated with ABCR gene mutations.[108] The ABCR protein is retina-specific and mutations of the ABCR gene may account for 3% of AMD cases.[2,105]

Shroyer et al. examined families that manifest both STGD and AMD. Using a direct-sequencing mutation

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detection strategy, they found that patients who were relatives of STGD subjects and who developed AMD were more likely to be carriers of pathogenic STGD alleles than predicted by chance alone.[109] In another study, screening of 1218 unrelated AMD patients and 1258 controls from North America and Western Europe identified two important variants in ABCR gene (G1961E and D2177N) that were statistically significantly related to AMD ($p < .0001$). There was a three-fold increased risk for AMD in D2177N carriers and a five-fold risk in G1961E carriers.[105] Several other population-based association studies have yielded negative results for associations between AMD and ABCR gene mutations when cases were compared to controls.[108,110–113]

Chromosome 1q: The Complement Factor H Gene (CFH): Its Role in the Inflammatory Reactions in the Pathogenesis of AMD

The complement factor H (CFH) gene produces a protein that inhibits the complement cascade.[114] Mutations of this gene may cause loss of inhibition of the complement system and as a result, the complement system is activated and may damage the RPE. The CFH gene is located on chromosome 1, in the region 1q25-31 that harbors the ARMD1 locus. This region has been repeatedly linked to AMD in familial and population-based association studies.[100]

In 2005, three groups identified a CFH variant that increased the risk of developing AMD.[76–78] Klein et al. performed a genome-wide screen of 96 cases and 50 controls for polymorphisms associated with AMD. Among 116,204 SNPs genotyped, an intronic variant of the CFH gene was associated with 7.4-fold increased risk for AMD in individuals homozygous for the risk allele.[78] Edwards et al. found similar results when this SNP was tested for association with AMD in two independent case-control populations. They added that the presence of at least one histidine at amino acid position 402 increased the risk of AMD 2.7-fold and may represent 50% of the attributable risk of AMD.[77] Haines et al. reported similar results.[76] The most commonly documented risk-conferring single-nucleotide polymorphisms (SNP) was a thymine (T) → cytosine (C) substitution at nucleotide 1277 in exon 9, which results in a tyrosine-to-histidine change at amino acid position 402 (Y402H) of the CFH protein.[76] This variant is located within binding sites for heparin and C-reactive protein.[115–118] This common variant explains approximately 43% of the AMD cases in older adults and may confer particular risk in the presence of environmental and genetic stimulators of the complement cascade.[76,119,120]

Zareparsi et al. showed that individuals with AMD who had at least one copy of the C allele of Y402H had significantly increased risk of disease (OR 2.98) compared with cases with the T allele. This genetic variant is related to both forms of late AMD.[41,80,121,122] A recent meta-analysis also found strong evidence for this association. Patients having CC and TC genotypes are roughly 6 and 2.5 times more likely to have AMD, respectively, than patients with TT genotype, suggesting a co-dominant, multiplicative genetic model.[123]

The roles of genes and environment together have been evaluated in a few studies. Seddon et al. showed that CFH is related to both geographic atrophy and neovascular disease after controlling for environmental risk factors, and smoking and BMI both increase risk after controlling for CFH genotype.[41] In this study, there was a statistical interaction between BMI and the CT and CC genotypes of the CFH gene. The attributable risks associated with the C allele plus adverse categories of the environmental factors were as high as 73%. Among those with the CC genotype, risk rose from 8- to 10- fold with smoking, and from 4- to 6-fold with higher BMI, compared to non-smokers or lower BMI, respectively.[41] Schmidt et al. also demonstrated that a genetic susceptibility combined with a modifiable lifestyle factor such as cigarette smoking gives a significantly higher risk of AMD than either factor alone. In this study, it was found that CFH and LOC387715 variant genes combined with cigarette smoking explained 61% of the population-attributable risk of AMD.[124] Smoking 10 pack-years or more and having the CFH CC genotype was estimated to increase risk of neovascular AMD 144-fold compared with smoking less than 10 pack-years and having the CT or TT genotype.[125]

The contribution of the Y402H polymorphism to exudative AMD susceptibility has been demonstrated in French, Italian, Russian, Indian, British and isolated Finnish populations.[126–131] The contribution of this allele was much lower in a Chinese population. Despite this, the polymorphism is significantly associated with neovascular AMD among Chinese patients.[132] In one Japanese population, CFH gene polymorphism was not associated with AMD.[133] Among Latinos, the CFH Tyr402His polymorphism was not a major risk factor for

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early AMD, but a subgroup of these cases with bilateral, intermediate-to-large soft macular drusen was 1.7 times more likely to carry either the homozygous or heterozygous His402 genotype.[134]

Other variants in the CFH gene have been found to modify the risk for AMD.[80,135,136] Hughes et al. identified a common haplotype associated with decreased risk of AMD. Twenty percent of elderly controls with no signs of AMD carried a deletion of CFHR1 and CFHR3 compared to 8% of individuals with severe neovascular AMD.[136] Maller et al. identified a new non-coding variant in CFH in a case-control study from a large US-based population of European descent, associated with disease risk of AMD. These authors also demonstrated the association with the previous CFH and LOC gene variants, and confirmed for the first time the association between AMD and the BF/C2 locus.[80]

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Chromosome 3p: CX3CR1 Gene

The CX3CR1 gene is a chemokine receptor expressed in retinal cells. It is thought that reduced CX3CR1-related cellular activities increase the risk for AMD. An association between two SNPs in CX3CR1 and AMD was demonstrated in two studies. It was found that CX3CR1 transcripts are diminished in the macular lesions of AMD patients. The M280 allele, one of the SNPs identified, resulted in aberrant CX3CR1 and CX3CL1 (ligand) interaction and lower expression of macular CX3CR1.[137,138]

Chromosome 6p

The Human Leukocyte Antigen (HLA) Genes

HLA polymorphisms influence the development of AMD, possibly modulating choroidal immune function. Different studies have found positive and negative associations between HLA alleles and AMD. In a population-based study in the UK, three alleles showed evidence for association with AMD. Allele Cw*0701 correlated positively with AMD ($p = 0.036$), whereas alleles B*4001 ($p = 0.027$) and DRB1*1301($p = 0.009$) were negatively associated. These HLA associations were independent of any linkage disequilibrium.[75]

Factor B (BF) and Complement Component 2 (C2)

BF and C2 genes are located in the major histocompatibility complex class III region. Haplotype analyses of these genes have identified a statistically significant common risk haplotype (H1) and two protective haplotypes (H10 and H7). Variants in H10 (L9H variant of BF and E318D variant of C2) and H7 (variant in intron 10 of C2 and R32Q variant of BF) conferred a significantly reduced risk of AMD. A combined analysis of the C2 and BF haplotypes and CFH variants demonstrated that variation in the two loci may predict the clinical outcome in 74% of the affected individuals and 56% of the controls.[79] Maller et al. reported confirmation of these results in an independent group of late AMD cases and controls.[80]

Vascular Endothelial Growth Factor (VEGF)

VEGF may play a role in the risk of developing AMD, especially the exudative form. The strongest association signal has been found at VEGF SNP hCV1647373 ($p = 0.001$). In this study, eight candidate genes for AMD (alpha-2-macroglobulin, creatine kinase, angiotensin-converting enzyme, interleukin-1alpha, low-density lipoprotein receptor-related protein 6 [LRP6], microsomal glutathione-S-transferase 1, VEGF, and very low density lipoprotein receptor [VLDLR]) were tested for genetic linkage and allelic association. It was found that only LRP6, VEGF, and VLDLR may play a role in the risk of developing AMD.[139]

Chromosome 6q: ELOVL4

Mutations in a photoreceptor cell-specific factor involved in the elongation of very long chain fatty acids (ELOVL4) are associated with STGD3 (autosomal dominant Stargardt-like macular degeneration), adMD (autosomal dominant atrophic macular degeneration), and pattern dystrophy. Ayyagari et al. found 11 ELOVL4 sequence variants in AMD patients but there was no association with their AMD status.[140] In a subsequent study, one of these variants, Met299Val, was significantly associated with AMD in case-control allele, case-control genotype and case-control family association studies.[141] However, additional research failed to demonstrate an association between ELOVL4 gene mutations and AMD.[142]

Chromosome 10q26

Three loci on chromosome 10q26, PLEKHA1, LOC387715, and HTRA1 have been linked to AMD in independent studies.[101,102,143,144] PLEKHA1 encodes

a pleckstrin homology domain, LOC387715's function is unknown to date, and HTRA1 encodes a secreted serine. Jakobsdottir et al. found the SNP rs10490924 within the PLEKHA1/LOC387715 gene as the second major locus for AMD. They estimated it to confer a population attributable risk of 57%.[102] However, a recent study by Yang et al. found the SNP rs11200638 within the promoter region of HTRA1 was the most likely causal variant for AMD in this region. They estimated it to confer a population attributable risk of 49.3%.[143] Dewan et al. found similar results in a Chinese population. They added that individuals with the risk-associated genotype have 10 times increased risk of developing wet AMD compared to individuals with the wild-type genotype.[144]

The HTRA1 protein appears to regulate the degradation of ECM proteoglycans. Overexpression of this protein appears to alter the integrity of Bruch's membrane, allowing invasion of choriocapillaris across the ECM. HTRA1 also binds and inhibits transforming growth factor-ß, an important regulator of ECM deposition and angiogenesis.

In a study of 457 patients with mainly non-advanced AMD, individuals with one or two copies of the LOC387715 A69S gene were 2.4 and 5.7 times more likely to develop AMD. Cigarette smoking and obesity increased the risk.[145] In a study of the LOC387715 A69S variant with 530 advanced dry and wet cases of AMD, similar to CFH, [41] cigarette smoking and BMI increased risk of late AMD independent of the LOC gene. The odds ratio was 12.1 for the homozygous TT risk genotype, controlling for other risk factors. There was no interaction found between smoking or BMI and the LOC variant.[146]

One prospective analysis showed that both LOC387715 A69S and CFH Y402H variants were independently associated with increased rates of progression from early and intermediate forms of AMD to advanced stages of the disease with visual loss, controlling for smoking and body mass index and other factors.[147]

Chromosome14q: Fibulin-5 (FBLN5)

Fibulin-5 is an ECM glycoprotein that participates in elastogenesis. This protein is localized to Bruch's membrane and the choriocapillaris in normal eyes. Missense mutations in FBLN5, but not in Fibulin-1, 2 or 4, have been reported to be associated with AMD.[97] In eyes with AMD, fibulin-5 has been found in the basal deposits of the RPE cells and in small drusen. This suggests that mutated fibulin-5 alters elastogenesis and may promote extracellular deposit formation in AMD.[148,149]

Chromosome 19q: Apolipoprotein E (ApoE)

ApoE is a major transporter of lipids and cholesterol in the nervous system. This protein is not specific to the retina. It has been associated with Alzheimer's disease. The ApoE4 allele has been shown to be a risk factor for Alzheimer's and protective for AMD. This genetic association suggests a possible common pathway in diseases of age and in their interaction with human genetic polymorphisms.[2] In one study, a variant of this gene, the ApoE C112R/R158C SNP, was found to decrease the risk for AMD. ApoE112R allele frequency was 10.9% in the AMD group, 16.5% in younger controls and 18.8% in clinically screened controls. A meta-analysis of eight cohorts including 4,289 subjects showed a strong association between AMD and 112R, but not 158C.[150]

In another study it was found that individuals with an epsilon2 genotype at the ApoE gene had a 4.8-fold increased relative risk of developing AMD compared to individuals with an epsilon4 genotype and a three-fold increased relative risk compared to individuals with an epsilon3 genotype. This finding was present only in females that had progression of AMD. This suggests a possible gender-specific role in AMD progression in patients with an epsilon2 allele.[151] Some familial, population-based studies and linkage analyses have failed to demonstrate the association of ApoE and AMD.[141,152–156]

Chromosome 19p: Complement Factor 3

Two independent studies reported the association of complement factor 3 with AMD. Maller et al. evaluated 1238 advanced cases of AMD with geographic atrophy and neovascular disease and 934 controls from the US,[157] and Yates et al. evaluated cases of mixed types of maculopathy from England and Scotland.[158] Odds ratios for the homozygous GG genotype for the C3F allotype ranged from 2.9 to 3.3 compared with the CC genotype.

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CONCLUSION

The prevalence of AMD has been increasing over the past few decades worldwide.[159,160] This increase in the prevalence has also been observed in racial groups not previously considered to be at risk.[161] This may be due to changing environmental risk factors, such as smoking and diet, improvements in assessment and diagnosis, or increased longevity of the population.

AMD is caused by a combination of environmental components and genetic predisposition. For instance, variants in the CFH and LOC387715 genes increase risk independent of modifiable risk factors, and environmental factors, particularly obesity and smoking, increase risk independent of these genetic variants. Identifying the genetic factors involved in the pathogenesis of AMD may eventually lead to screening of high-risk individuals to facilitate earlier diagnosis, to prevent disease or decrease severity, and improve therapeutic options.

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