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Genetics of Immunological and Inflammatory Components in Age-related Macular Degeneration

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Abstract

Age-related macular degeneration (AMD), affecting 30 to 50 million elder individuals worldwide, is a disease affecting the macular retina and choroid that can lead to irreversible central vision loss and blindness. Recent findings support a role for immunologic processes in AMD pathogenesis, including generation of inflammatory related molecules in the Bruch's membrane, recruitment of macrophages, complement activation, microglial activation and accumulation in the macular lesions. Pro-inflammatory effects of chronic inflammation and oxidative stress can result in abnormal retinal pigment epithelium, photoreceptor atrophy and choroidal neovascularization. The associations of immunological and inflammatory genes, in particular the genes related to innate immunity with AMD support the involvement of various immunological pathways in the AMD pathogenesis. We review the literature on the involvements of inflammatory genes in AMD, highlight recent genetic discoveries, and discuss the potential application of such knowledge in the management of patients with AMD.

Keywords

age-related macular degeneration (AMD); complement factor; cytokine/chemokine; gene; innate immunity

Age-related macular degeneration (AMD) is a neurodegenerative disease of the central retina (the maculae) that represents the most common cause of irreversible visual impairment among people over age 50 in the world. Risk is multifactorial, relating to age and various environmental, dietary, and genetic factors. Heterogeneity of disease phenotype and onset late in life has complicated the disease mechanism. However, advances in genetic epidemiology and technology have recently transformed our understanding of heritable risk factors and provided insights into AMD pathophysiology. While AMD is not a classical inflammatory disease and inflammatory cells are reduced compared to other inflammatory tissues or are even neglected in these lesions, macrophages and even lymphocytes have been found in AMD lesions.[1] There is a growing body of evidence suggesting an important role of inflammatory and immunological events in AMD pathogenesis.[2–4]

Clinical and histopathological hallmark of AMD is macular atrophy with drusen. Clinically, drusen are subretinal, discrete or soft yellowish lesions. Histopathologically, drusen are

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pancake-shaped, amorphous eosinophilic materials in Bruch's membrane beneath retinal pigment epithelial cells (RPE),[3] Biochemically, drusen contain lipids, proteins.[5–7] and oxidation products from lipids and carbohydrates.[6,8] These components from oxidative modifications in drusen and Bruch's membrane can activate pattern recognition receptors that initiate inflammatory and immune responses.[9] Large drusen and greater number of drusen in the maculae may develop geographic atrophy ('dry' AMD) and choroidal neovascularization CNV) or exudative/neovascular AMD ('wet' AMD). Drusen and the retinal lesions in advanced AMD can initiate and promote inflammatory responses, as well as innate and adaptive immune reactions, such as macrophage recruitment, microglial accumulation, complement activation, cytokines/chemokines releasing, and inflammatory oxidative stress.

Studies on twins and affected families have long suggested a heritable component to AMD risk.[10,11] Genetic linkage studies found disease susceptibility loci on chromosomes 1q25–31 and 10q26.[12] In the past 7 years, genome-wide and targeted genetic association studies have identified various polymorphisms important for AMD susceptibility.[13–19] Notably, many of them are immune-related genes, including complement system, e.g. factor H (CFH), complement component 2 (C2), complement component 3 (C3), complement factor B (FB), and complement factor I (FI); toll-like receptor (TLR), e.g., TLR-3 and TLR-4; and chemokines, e.g., CX3CR1 and CCR3. However, controversies have been raised over the associations of TLR and AMD.[20–22]

I. AMD ASSOCIATED IMMUNOLOGICAL GENES IDENTIFIED BY LINKAGE AND FAMILY-BASED STUDIES

Data from most family studies of AMD have supported a strong genetic component to disease.[23–25] Linkage studies have suggested several chromosomal regions that may harbor AMD susceptibility genes. Klein and colleagues were the first to map a susceptibility locus, ARMS1, to chromosome 1q25–q31 in a large pedigree with predominantly geographic atrophy AMD.[24] This locus includes CFH.

Recent studies identified several candidate loci. Weeks et al reported potential loci on chromosomes 1q31, 9p13, 10q26, and 17q25.[23] These results corroborate with Klein et al,[24] in which linkage to chromosome 1q25–q31 shows an LOD score >1.5. Several of the following studies also confirmed the linkage on chromosome 1, mapping between 1q25–31.[10–12] Schick et al. performed a genome-wide scan of 102 families from the Beaver Dam eye study and did not find a strong signal on chromosome 1, but reported 12q23–24, near D12S346, to have the strongest signal.[26] Other potential regions included 5q12–13, 6q14–21, 15q11–14, 15q25–26. D5S2500, on chromosome 5, D12S1300 and PAH on chromosome 12, had all been previously reported.[23] Seddon et al found significant linkage on chromosomes 2, 3, 6, and 8, in addition to 1, 10, 12, 16, 22, X.[11] Mejewski et al studied 70 large families and found evidence for linkage in five regions with scores exceeding LOD = 2 − 1q31, 3p13, 4q32, 9q33 and 10q26.[10] Several of these regions are close to the chromosomal position of candidate immune genes associated with AMD (Table 1). Iyengar et al performed a genome wide scan on 34 extended pedigrees and had their strongest signal at 15q14, and observed 13 other regions on 11 chromosomes,[27] many of which were also consistent with previous reports. Abecaiss et al performed a genome wide scan of 412 affected relative pairs and found linkage in 5 regions: 1q41, 2p25, 5p13–14, 9q31, 22q12.[28]

Both 1q15–31 and 10q26 have showed the most consistency and have since been validated.[10,11,24,29] Region 1q15–31 has shown implication in at least 5 studies and 10q26 also been implicated in several studies. Since these studies, CFH at 1q32 has been shown to

be associated with AMD. In addition, HTRA1 and ARMS2/LOC387715, located at 10q26, show strong association with AMD (Table 1).

Several other linkage studies have searched for new candidate genes. With evidence suggestive of another AMD locus on chromosome 16p12, one group studied five genes within this locus – CACNG3, HS3ST4, IL4R, Q7Z6F8, ITGAM. The strongest evidence for linkage was within CACNG3. After adjusting for known AMD risk factors, rs2283550 remained the most strongly associated SNP.[30] One linkage study reported SKIV2L and MYRIP as protective factors for AMD.[31] In addition, LIPC and TIMP3 were suggested to be associated with AMD.[32] A susceptibility locus was identified near TIMP3, which is an extracellular matrix metalloproteinase that has been implicated in early onset maculopathy.[33] The association of loci within LIPC and AMD has suggested a connection between HDL metabolism and AMD pathogenesis.

These studies have shown that the use of families with significant history of AMD has also been quite effective in the discovery of genes associated with AMD. However, evaluation of the genetic basis of AMD through family studies has its challenges. Many individuals in a family are older and may have died, or they suffer from a multitude of other diseases that complicate results. In addition, many members may be younger and have not developed signs of macular degeneration. Therefore, several generations of informative individuals are not easily available.

II. AMD ASSOCIATED IMMUNOLOGICAL GENES IDENTIFIED BY GENOME-WIDE AND CANDIDATE GENE ASSOCIATION STUDIES

Genome-wide association study (GWAS) studies have revealed CFH to have a strong association to AMD.[13,15,34] Studies have shown an increase risk of AMD in individuals with a T>C substitution in exon 9 of CFH representing a tyrosine-histidine change at amino acid 402 (Y402H). This polymorphism has been located to a region of CFH that binds heparin and C-reactive protein.[13,35] Another study found association of 8 common SNPs in the CFH gene, with two missense mutations exhibiting high significance to AMD: 162V and also the Y402H variant.[15] The strongest association was found for the synonymous A473A (rs2274700:G>A) variant in exon 10 with an odds ratio of 3.42, 95% CI 2.27–5.15. These SNPs have been confirmed in numerous studies.[16,36–38]

At least 9 of the loci encode proteins of the immune-related pathways found to be associated with AMD–CFH, FB/C2, C3, C5, human leukocyte antigen (HLA) locus, CX3CR1, CCR3, and TLR3, TLR4 (Table 1). Therefore, the immune system is proposed to play a central role in the pathogenesis of AMD. CFH is an important regulator of the complement system. The activation of the alternative complement cascade is initiated by the formation of the C3Bb complex, also known as C3 convertase (Figure 1). Formation of this complex leads to the development of the terminal complex and amplification of the immune response. The dissociation of this C3Bb complex is accelerated by CFH. Therefore, alterations in the structure of CFH can lead to abnormal or increased immune activity. Studies have implicated local inflammation and activation of the complement cascade in the formation of drusen, a hallmark of early AMD.[39] Similar inflammatory mechanisms have been reported in relation to formation of extracellular plaques in Alzheimer's disease and deposits in atherosclerosis.[39,40]

Both components of the complement system have been found in drusen of AMD patients and have been shown to contribute to vascular endothelial growth factor (VEGF) expression, a signal for angiogenesis.[41] Recent GWAS studies have further confirmed the association of C3 with AMD.[20] FB and C2 genes were associated with decreased susceptibility to

AMD.[42–44] FB and C2 function as activators of the alternative and classic complement pathways, respectively. If their enzymatic activity is reduced due to alterations in protein structure, then these alternations may provide a lower risk of chronic complement activation and therefore, a decreased risk of AMD.

Different variants within C3 and FB/C2 have been identified to be associated with AMD.[42–45] The R32Q variant of FB showed protective from AMD in a family based study. Three SNPs in C2 and FB were strongly associated with decreased risk of AMD in a case-control study.[44] The minor alleles at C2 rs547154 and FB R32Q were present in 4% of cases versus 10% of the controls.[44] Complement C3 S/F (Arg80Gly) also showed strong evidence of an association with AMD.[45] These studies further support the role of the complement pathway in AMD development. However, functional studies are needed to confirm the protective effects of these genes on AMD development.

Other immune-related genes associated with AMD are CX3CR1, likely related to the recruitment of macrophage and microglia. Three independent studies showed a mild association of *CX3CR1* variants with AMD.[46–48] However, Ryu et al did not find this association in a recent GWAS study.[20] On another recent large population of 1,093 neovascular AMD patients compared to 396 controls in France, no association was reported.[49] Takeda et al. reported that CCR3, an eosinophil/mast cell chemokines receptor, was highly expressed in human CNV membrane, but not in normal vessels. These authors suggested that CCR3 could be an early marker of and potential therapeutic target for CNV.[50] However, Li et al demonstrated no inhibitory effect of CCR3 antibody on CNV using the matrigel induced model in mice and rats.[21]

III. GENE–ENVIRONMENT AND GENE–GENE INTERAC TIONS

AMD is a complex multifactor disease involving both genetic and environmental risk factors. Studies have shown that gene-gene and gene-environment interactions play a role in disease risk. These interactions have been studied in order to provide further information about the contribution of risk factors to the development of AMD. Of the environmental risk factors, age and smoking have been the most consistent.[32] Body mass index (BMI) has shown a marginal association.[51] It has been accepted for many years that the immune system undergoes changes resulting in loss of immune function with age. Smoking is known to weaken the immune system and has been confirmed as a risk factor for AMD. Patients have a 1.8-fold higher chance of AMD if they ever smoked compared to those who never smoked.[51] However, it still remains unclear as to the extent of their effect on AMD development. Weeks et al hypothesized that the effects of smoking on the risk of AMD is accentuated by a gene in region 10q26.[12] Since then, the joint effects of genetic and environmental factors are implicated to have a better prediction for advanced AMD.[52–58]

Schmidt et al found that smoking strongly modifies the association of LOC387715 and AMD and estimated that CFH, LOC387715 and cigarette smoking together explain 61% of the population-attributable risk of AMD.[53] Seitsonen et al found that smoking exerted an extra risk for AMD,[52] but seemed to only in connection with other factors such as sex and C3 genotype. Nakanishi et al studies suggested interactions between CFH Y402H and cigarette smoking.[57] Shaumberg et al also suggested interplay of genetic and environmental risk factors stating that patients homozygous for the risk alleles of CFH Y402H and LOC387715 A69S had a 50-fold increase in the risk of AMD and cigarette smoking and obesity multiplied the risk as well.[54]

As for gene-gene interactions, there have been differing conclusions. Chen et al found weak interactions between CFH rs1061170 and HTRA1/LOC387715 rs10490924 as well as between CFH rs2274700 and HTRA1/LOC387715 rs10490924.[51] This result was also

similar in a study in Finland, which showed a possible interaction between CFH and LOC387714.[52] However, other studies have not found this interaction.[18,53,56,59,60] The intricate interplay of genetics and environmental factors will need to be further studied in order to better understand people's risk for AMD.

IV. DISTINCT AMD LOCI IN ETHNIC GROUPS

Several studies have looked at specific populations to determine if the susceptibility genes could be generalized to different locations and ethnicities or if other genes played a more significant role. For example, in a French population PLEKHA1 (rs4146894), HTRA1 (rs11200638) and ARMS2/LOC387715 (rs10490924) were found to be independently and strongly associated with exudative AMD.[61] A study of an Indian population validated the association of risk alleles within ARMS2/LOC387715 (rs10490924) and HTRA1 SNPs (A allele: rs11200638 and C allele: rs2672598), along with risk estimates among Indian patients with AMD.[62] A study found statistically significant associations of three SNPs of ARMS2/HTRA1 region: rs3793912, rs10490924, rs11200638 and AMD in Japanese population.[63] Chu et al found CFH and HTRA1 polymorphisms to be potentially additive contributors to exudative AMD in the Han Chinese population.[64] Another study focusing on a separate group of Singaporean Chinese indicated that the TLR3 rs3775291 is not associated with CNV and polypoidal choridal vasculopathy (PCV), a condition similar to but distinct from AMD.[65]

V. COPY NUMBER VARIATION OF IMMUNE RELEVANT GENES AND AMD

Although numerous SNPs have been discovered to be highly associated with AMD, they do not account for the entire genetic component of the disease. Interindividual variation in human genome exists not only in the sequence level but also in other structures. Deletions and duplications can result in alterations in the copy number of affected segments of the human genome.[66] Copy number variation usually refers to large repeated regions of more than several hundred nucleotides and distinguishes from microsatellites and minisatellites.[67] Copy number variation deviated from normal two copies could be dialleletic or multialleletic. However, due to the lack of accurate technique, copy number variation genotypes are often reported as "gain" or "loss" relative to dialleletic type. Population-based studies have identified thousands of copy number variation loci throughout the human genome.[67,68] The proposed mechanisms on copy number variation impact include gene dosage, gene interruption, gene fusion, and positional effects.[69] Copy number variation of dosage-sensitive genes may cause or predispose to a variety of human diseases. The association of copy number variation have been reported with disease susceptibility, among most of which were immune related disorders including glomerulonephritis,[70] psoriasis,[71,72] systemic lupus erythematosus,[71,73–75] and HIV.[76]

While copy number variation contributes to the susceptibility of various human diseases, only a limited number of studies on its role in AMD pathogenesis were reported. GWAS failed to identify any copy number variation loci associated statistically significant with AMD; however, those studies spotted several rare copy number variations close to or in known AMD susceptible genes such as EFEMP1.[77–80] Moreover, direct sequencing of the targeting loci and multiplex ligation-dependent probe amplification was able to find common deletions in *CFH related genes 1* and *3* (*CFHR1* and *CFHR3*), which are protective against AMD.[38,81–83] Individuals who carry the homozygous deletion had no detectable CFHR1 protein in their serum, indicating the functional importance of the structural variation, and showed no evidence of AMD. Even though the boundary of the deletion has not been precisely determined yet, it lies within the regulators of complement activation locus on chromosome 1q32. Combination of two large cohorts in Caucasian recorded a 5.7%

of frequency of the homozygous *CFHR1* deletion in the non-AMD population with an odds ratio of 0.191 to AMD.[81] The deletion of *CFHR1* allele also displays considerable variation between racial/ethnic groups. Homozygotes are most common in African Americans (16%), less common in Hispanics (6.8%). The district distribution of this protective factor between ethnic groups is in agreement with the low frequency of late-onset AMD in African Americans, compared to the Caucasians.[84]

When there is no clue to the potential contributor of copy number variation of any genes in AMD pathogenesis, it is logical to place the precedence for exploring copy number variations of genes that have been identified to be SNP-AMD-associated. Similar approach has been demonstrated to be successful in the study of α-synuclein gene in Parkinson's disease.[85,86] There is also evidence for linkage disequilibrium between copy number variations and SNPs in human genome.[87] We performed quantitative copy number genotyping for several AMD genes in neovascular AMD patients and elderly controls.[88] Among 6 AMD relevant genes, *CCR3, CFH, CX3CR1, VEGF, ERCC6, and HTRA1*, 4 of them function as immune molecules. By analyzing 131 persons with neovascular AMD and 103 elderly persons without AMD, we found that copy number variations of above genes existed in both AMD and control populations. As estimated by a maximum likelihood algorithm, based on the probability density distribution across all samples, the copy number variation = 2 was the predominant copy number genotype of all copy number variations of the tested genes. Novel copy number variations were found within *CCR3* and *CX3CR1*. Even though the copy number variations of the tested genes did not differ between the AMD and control after strict statistical justification, there were trends in the unadjusted data suggesting that *CX3CR1* might be a gene of interest in terms of copy number variation. The rates of copy number = 3+ carriers for CX3CR1 were 25.0% in AMD and 14.6% in controls (OR = 0.52, 95% CI: 0.27–1.01, p = 0.05), indicating a protective role of the extra copy of *CX3CR1* for AMD.[88] The result is in agreement with previous reports that two loss-of-function SNPs in *CX3CR1* are associated with moderately elevated AMD risk.[46–48] In addition, mice with *Cx3cr1* or *Cx3cr1*/*Ccl2* being knocked out develop spontaneously AMD-like pathological features in retina.[46,89,90]

VI. PHARMACOGENETICS OF IMMUNE RELEVANT GENES AND AMD

In the past decade, some new treatment and prevention options have been introduced in an attempt to minimize the AMD-induced damages. A high-dose of an orally administered combination of the vitamin C, vitamin E and beta-carotene, in addition to copper and zinc, is a widely accepted preventive approach.[91] Thermal laser photocoagulation and verteporfin photodynamic therapy (PDT) are also the extensively used options.[92] Currently, the most widely utilized therapy for neovascular AMD is intravitreal administration of anti-VEGF antibodies. However, patients do not equally respond to these treatments. Some suggested that the AMD-susceptibility SNPs or even SNPs in genes functioning in the therapy-related pathways are responsible for the differentiated responses.[93–100]

A study on the interaction between the CFH Y402H/ARMS2 A69S variants and supplementation with antioxidants plus zinc found that in individuals with homozygous CFH non-risk variant (402YY), 34% in the placebo group progressed to advanced AMD, compared with 11% in the antioxidants plus zinc-treated group: a reduction of approximately 68%. Of those individuals with the homozygous CFH risk variant (402HH), 44% in the placebo group progressed to advanced AMD, compared with 39% in the anti-oxidants plus zinc-treated group: a reduction of only 11%, indicating that CFH non-risk variant carriers have a better response to the intervention than risk variant carriers. In addition, a similar interaction was observed in the groups taking zinc alone versus those taking no zinc. Of those 402YY carriers, 36% in the no zinc group progressed to advanced

AMD, compared with 14% in the zinc-treated group; a reduction of 61%. Of those 402HH carriers, 47% in the no zinc group progressed to advanced AMD, compared with 42% in the zinc-treated group; a reduction of only 11%.[98] The study did not find interaction between the ARMS2 A69S variant and the AREDS treatment, indicating that inflammatory factors are not only involved in the AMD susceptibility but also in individual's response to nutrient supplements. Specific biological mechanisms have not yet explained the interaction and that CFH variants had an altered binding affinity to zinc.[101]

Another study found that individual's carrying non-risk CFH 402YY had worse outcomes than that of risk CFH 402 carriers after PDT.[102,103] Among the 27 patients eligible to PDT, the average visual loss following PDT was 70 letters in 402YY carriers (n = 2), of 3.5 letters in 402YH carriers (n = 12) and 12 ETDRS letters in 402HH carriers (n = 13).[102] Two independent studies exhibited similar results in terms of average post-PDT visual acuity and proportion of responders.[99,104,105] Interestingly, patients with unfavorable genetic makeup for AMD may have better outcome after PDT. One explanation is that patients with the non-risk CFH variant may develop CNV by other non-inflammation mechanisms rather than complement factors, and this makes them less responsive to PDT.[105] Another AMD-susceptibility SNP, ARMS2 A69S, did not show any modifying effect on the PDT therapy.[105]

VEGF is recognized as a key mediator in the CNV formation during AMD development. Poor visual acuity after anti-VEGF therapy was found in AMD patients carrying risk CFH 402HH compared to the other CFH402 genotypes combined after giving bevacizumab. However, there was no association between the response to bevacizumab and ARMS2 A69S genotypes. [99] A similar study on exudative AMD treated with ranibizumab found that CFH 402HH carriers had a 37% higher chance of requiring additional ranibizumab injections because of recurrence.[96] Even though different outcomes were adopted in evaluation, similar relationships were identified in a prospective study, which observed a significantly worse outcome for distance and reading visual acuity in the CFH 402HH genotype group.[100] However, a recent study reported a trend of more favorable visual acuity outcomes after 6 months of intravitreal ranibizumab therapy in patients carrying AMD risk-variants of CFH, VEGF and HTRA1,[106] which is controversial to previous studies.[96,99,100] No explanation for this discrepancy was offered in the study.[106]

Instead of only focusing on the SNPs with AMD susceptibility and the outcomes of anti-VEGF therapy, we recently conducted a study to determine pharmacogenomic mechanism of some competent immunological molecules among others, including *CFH, HTRA1*, *IL-17, IL-23R*, *CYP3A*, *LEP and VEGFA*. Initial data indicated a trend of association of an IL-23R SNP in the response to anti-VEGF therapy. This result echoes a novel finding of the involvement of IL-17 pathway in AMD pathogenesis.[107]

While the concept of AMD pharmacogenomics is promising, the progress in this field is lagging. The available literatures on this field are based on studies with small sample size, heterogeneous study participants and non-standardized therapy protocol. The definitions for therapy response are ambiguous and long-term follow-up is lacking. The study in retrospective design is another problem. Moreover, when majority focusing on the interaction of AMD-susceptibility SNPs with therapeutic responses, it should be understood that possible genetic components on the therapy responses might not be necessarily associated with the disease susceptibility itself. Some studies selected genes functioning in the activation of therapy-induced pathways to test the possible modifying effect. As cited before, SNPs in coagulation balance genes (factor V, prothrombin) may affect the efficacy of PDT.[93,95] Similar approaches can be used by carefully selecting functional variations in the inflammation related genes and test their role in therapy responses.

VII. AMD AND IMMUNE REGULATION BY EPIGENETICS AND MicroRNAS

In general, epigenetics refers to the study of heritable changes in gene expression caused by mechanisms other than changes in DNA sequence. Examples of such changes are DNA methylation and histone acetylation, both of which suppress gene expression. The influence of epigenetic changes in common complex diseases has been extensively reported.[108] Collective evidence indicates modulations of environmental pressure on gene expression in the immune system through epigenetic mechanisms.[109] However, thus far, there is no peer-reviewed full article published on epigenetics and AMD. Two presentations in ARVO 2011 demonstrated an altered epigenetic profile of immune genes in ocular tissue from AMD patients by large scale epigenetic array. One of the studies applied a twin-based design by recruiting two pairs of monozygotic twins with discordant AMD pathology. Among 2.1 million gene promoters, the study identified ~1000 candidate genes within which promoters differential DNA methylation patterns were found. Among those 1000 genes, 256 genes were associated with hypomethylated CpG sites, while 744 genes with hypermethylated CpG sites were only in twins with AMD. One exemplar locus of those differentially methylated loci is within *CCL22* locus. Hypermethylated CpG sites were only found in control but not AMD twins, indicating a potential role of CCL22 in AMD.[110]

MicroRNAs (miRNAs) are non-protein-coding RNAs and functions as post-transcriptional regulators that bind to complementary sequences on target mRNAs. miRNA usually functions as translational repressor and gene silencing. The human genome may encode over 1000 miRNAs and target about 60% of mammalian genes.[110] miRNAs appear to regulate the innate and adoptive immune systems. Aberrant miRNA expression can contribute to pathological conditions involving the immune system.[111] A preliminary study described immune gene regulation by miRNA in retinal tissue.[112]

A study reported in ARVO 2011 found district patterns of miRNA expression in peripheral blood monocytes of geographic atrophy AMD patients. The study suggests the involvement of systemic immune responses in the pathogenesis and progression of geographic atrophy AMD.

Several animal studies reported the involvement of miRNAs in AMD relevant pathological features. Accumulation of miRNA in retina due to disruption of DICER1 can cause retinal lesion mimicking geographic atrophy AMD.[113,114] miR-23~27~24 gene clusters can regulate angiogenesis and choroidal neovascularization, since miRNAs encoded by the miR-23~27~24 gene clusters are enriched in endothelial cells and highly vascularized tissues.[115]

In summary, genetic studies have mapped genes in the complement pathway that are involved in the regulation of innate immunity with AMD susceptibility and pharmacogenesis. Majority of the association in complement genes have replicated in diverse populations worldwide. Gene-gene and gene-environment interactions are also found as significant covariates in AMD pathology. Studies of copy number variation, epigenetics and miRNA may provide further evidence on the underlying molecular genetic mechanisms in AMD.

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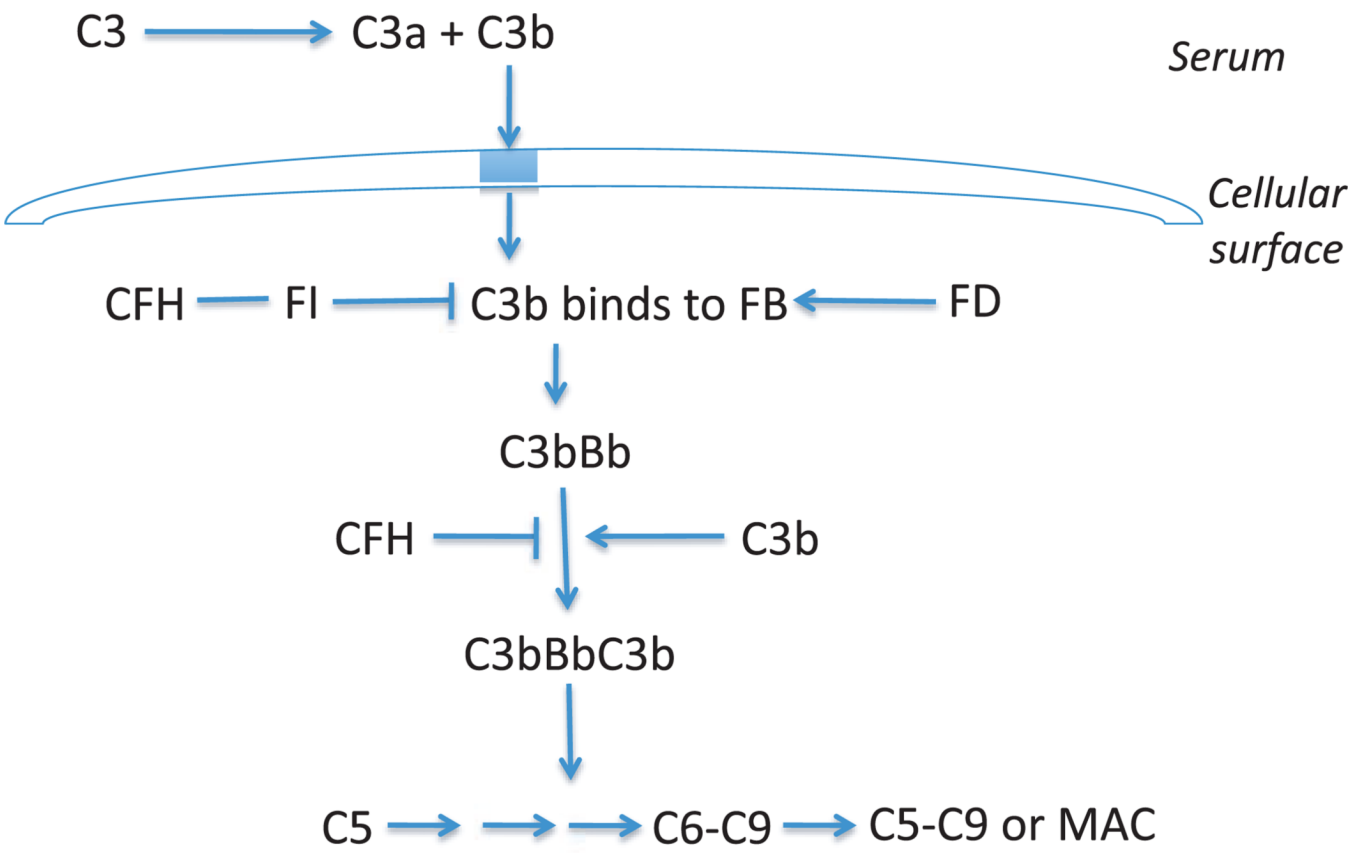

Figure 1.
Alternative Pathway C3, complement component 3; CFH, complement factor H; FI, factor I; FB, factor B; FD, factor D; C5, complement component 5; C6, component component 6; C9, complement component 9; MAC, membrane attack complex.

Table 1

Candidate immune genes associated with AMD.

Gene symbol (name)	Function	Chromosomal Position	Variant	Odds Ratios (OR)	References
CFH (Complement factor H)	Inhibitor of alternative complement pathway	1q32	rs1061170	OR_{hm} = 6.32	14, 16, 17
C2/CFB (Complement component 2/ Complement factor B)	Regulation of complement activation	6p21	rs9332739 (C2) rs4151667 (CFB) rs641153 (CFB)	OR_{ht} = 0.32–0.40	42, 44
CFHR1/CFHR3 (Complement factor H-related 1, 3)	Unknown, possible overlapping function with CFH	1q31-q32	84K bp deletion	OR_{hm} = 0.29	38, 83
C3 (Complement component 3)	Innate immunity (alternative complement pathway activator, classical pathway component)	19p13	rs2230199, rs1047286	OR_{hm} = 1.93–3.91	45
C5	Innate immunity (alternative complement pathway component)	9q33–q34	rs17611, rs7026551, rs7037673	OR_{hm} = 0.66O R_{hm} = 1.50O R = 0.51	116
HLA (Human leukocyte antigen) class I and II	Regulation of immune response	6p21.3	Cw*0701 DQB1*0303	OR_{hm} = 1.85O R_{hm} = 2.67	117
CX3CR1 (Chemokine [C-X3-C motif] receptor 1)	Inflammation (chemokine receptor)	3p21	rs3732378	OR_{hm} = 1.98–2.70	47, 48
TLR3 (Toll-like receptor 3)	Innate immunity (targets + viral dsRNA)	4q35	rs3775291	OR_{hm} = 0.44–0.61	19
TLR4 (Toll-like receptor 4)	Innate immunity (bacterial endotoxin receptor)	9q32–q33	rs4986790	Conflicting results:OR_{ht} = 2.65; no association	118, 119

OR_{hm} homozygous odds ratio for risk allele; OR_{ht} heterozygous odds ratio for risk allele