Title

Genetic insights into age-related macular degeneration: Controversies addressing risk, causality, and therapeutics

Journal

Molecular Aspects of Medicine, 33(4)

ISSN

0098-2997

Author

Gorin, Michael B

Publication Date

2012-08-01

DOI

10.1016/j.mam.2012.04.004

Peer reviewed

Published in final edited form as:
Mol Aspects Med. 2012 August ; 33(4): 467–486. doi:10.1016/j.mam.2012.04.004.

Genetic insights into age-related macular degeneration: Controversies addressing Risk, Causality, and Therapeutics

Michael B. Gorin, MD PhD[a,b]

[a]Harold and Pauline Price Professor of Ophthalmology, Departments of Ophthalmology and Human Genetics, David Geffen School of Medicine – UC – Los Angeles

[b]Jules Stein Eye Institute, 200 Stein Plaza, Los Angeles, CA 90095

Abstract

Age-related macular degeneration (AMD) is a common condition among the elderly population that leads to the progressive central vision loss and serious compromise of quality of life for its sufferers. It is also one of the few disorders for whom the investigation of its genetics has yielded rich insights into its diversity and causality and holds the promise of enabling clinicians to provide better risk assessments for individuals as well as to develop and selectively deploy new therapeutics to either prevent or slow the development of disease and lessen the threat of vision loss. The genetics of AMD began initially with the appreciation of familial aggregation and increase risk and expanded with the initial association of *APOE* variants with the disease. The first major breakthroughs came with family-based linkage studies of affected (and discordant) sibs, which identified a number of genetic loci and led to the targeted search of the 1q31 and 10q26 loci for associated variants. Three of the initial four reports for the *CFH* variant, Y402H, were based on regional candidate searches, as were the two initial reports of the *ARMS2/HTRA1* locus variants. Case-control association studies initially also played a role in discovering the major genetic variants for AMD, and the success of those early studies have been used to fuel enthusiasm for the methodology for a number of diseases. Until 2010, all of the subsequent genetic variants associated with AMD came from candidate gene testing based on the complement factor pathway. In 2010, several large-scale genome-wide association studies (GWAS) identified genes that had not been previously identified. Much of this historical information is available in a number of recent reviews.(Chen et al., 2010b; Deangelis et al., 2011; Fafowora and Gorin, 2012b; Francis and Klein, 2011; Kokotas et al., 2011) Large meta analysis of AMD GWAS has added new loci and variants to this collection.(Chen et al., 2010a; Kopplin et al., 2010; Yu et al., 2011) This paper will focus on the ongoing controversies that are confronting AMD genetics at this time, rather than attempting to summarize this field, which has exploded in the past 5 years.

Keywords

molecular genetics; Age-related macular degeneration; Association studies; Family-based linkage; Risk factors; Genetics-based therapeutics

Corresponding author: Michael B. Gorin, Office phone: 310 794-5400, Fax phone: 310 206-7826, gorin@jsei.ucla.edu.

Disclosures

Dr. Gorin is listed as a co-inventor on a patent held by the University of Pittsburgh and licensed to Ophtherion and Sequenom regarding “Susceptibility genes for age-related maculopathy (ARM) on chromosome 10q26”. US Patent Number: US 7,695,909 B2

1.0 Genetic Risk Factors for AMD

1.1 Family-based linkage and case-control association studies

It is widely reported that the genetic variants associated with AMD account for approximately 70% of the risk for the condition.(Seddon et al., 2009a; Spencer et al., 2011) In some studies the population attributable risk of multiple variants for AMD is as high as 87%.(Gibson et al., 2010) The contributions of genetics to AMD are largely based on odds ratios estimated from case-control association studies that are not exactly equivalent to relative risks. These estimates are primarily based on the cumulative contributions of common variants or SNPs on AMD risk but fail to capture the more elusive effects of many rare variants that may have a major impact on disease risk. Family-based studies have shown that the relative risk to a first degree relative is approximately 6- 12 times higher than that of the general population and that some families confer greater degrees of recurrence risk to relatives than others.(Klaver et al., 1998) One of the most important aspects of the genetics of AMD is that the current evidence for the basis for the genetic risk for individuals with a positive family history of AMD is very similar to the genetic risk factors that have been identified in persons with no known affected individuals within their families. Highly penetrant, rare variants may yet be responsible for some AMD families but we have only just begun to explore this avenue. To date, only one large AMD family has been attributed to mutations in a gene on 1q25.3, hemicentin-1 (*HMCN1*), which is not a major contributor to AMD risk based on case-control association studies. However, even in that family, it is impossible to be sure if the hemicentin-1 mutation was responsible for the disease, since that gene is in high linkage disequilibrium with the *CFH* locus on Chromosome 1q31 and thus one can't exclude another gene and mutation from causality. The recent report (Nakata et al., 2011) of a rare variant in the *CFH* gene that has been associated with hemolytic uremia syndrome and which has been found in a number of individuals with non-syndromic AMD, gives support to the existence of highly penetrant rare variants, but the extent to which this variant or similar ones in the *CFH* gene contribute to familial AMD cases is unknown.

While we know that two loci based on common SNP associations contribute to the greatest AMD risk (1q31 and 10q26), there is evidence from increasingly large case-control association studies to either confirm the association with other genes that have been implicated as candidate genes or identify novel loci as well as to suggest that there is genetic variation buried within the GWAS studies that contributes to AMD risk but which we cannot easily identify because of lack of a sufficient signal to be detected as statistically significant. For a GWAS case-control design the accepted threshold of significance is a p-value of less than 5×10^{-8}, dependent on the SNP platform. The list of AMD-associated variants and genes has continually grown during the past three years and has been summarized by a number of reports and recent reviews. (Chen et al., 2010b; Deangelis et al., 2011; Fafowora and Gorin, 2012a; Katta et al., 2009)

In this brief review, we have purposely not provided the various odds ratios that have been reported for the various AMD-related gene variants. These values are constantly shifting and vary based on the population that is studied as well as the phenotypic features of the AMD. More importantly, while odds ratios from case-control association studies are relevant to the relative magnitude of the impact that a particular variant may contribute to the risk of AMD, they are not equivalent to true measures of relative risk and are only a proxy for the population-based estimates of relative risk. Secondly, the odds ratios for a given variant and gene are not reflective of the importance of that gene with respect to the pathogenesis of AMD. There are likely to be genes whose protein products are critical to the development and progression of AMD but for which there are no common variants that impact its function. Alternatively a gene may greatly influence AMD risk as a result of numerous, rare

variants that would be overlooked by even a large case control association study. While we would not discount that both *CFH* and the *ARMS2/HTRA1* loci are major contributors to AMD risk and pathogenesis, some genes with much smaller odds ratios and larger p-values (assuming that they are still below the significance level) may still be appropriate targets for rare variant analyses and as targets for therapeutic interventions.

We do provide the Ensembl cytogenetic band locations for most of the genes cited within this review because in many cases, the evidence for an association of the gene with AMD has come from one or more SNPs within that region. Thus one can't exclude the possibility that other genes within those regions could be responsible or contribute to the observed association or linkage signal. These locations serve as a reminder that, in the absence of biological confirmation (which is available for only a limited number of AMD-related genes), an association with a SNP, whether in a family or in a case-control cohort, represents a genetic susceptibility location but does not necessarily imply that the SNP is causative.

The latest results are those emerging from a large, international collaborative effort, The AMD Gene Consortium project, comprised of 18 research groups. The study pooled GWAS data involving >7,600 cases and >30,000 matched controls and then collaborated on a replication effort of 32 SNPs involving >9,200 cases and >8,000 controls to achieve a composite analysis of >16,900 advanced AMD cases and matched controls. In addition to confirming 12 previously reported AMD susceptibility loci, six new loci were identified. This meta-analysis provides perhaps the best odds ratio estimates and gender difference for the Asian and European populations. Since the results of this work were not available for publication at the time that this review was prepared, the reader is referred to the upcoming publication from this group for details regarding p-values, odds ratios, risk prediction models, expression and pathway analyses, as well as ethnic and gender differences based upon the largest combined AMD genetic study to date. One goal of this collaborative effort is to strengthen the evidence for (or against) associations with previously reported loci. Thus a number of the unreplicated or weaker associations that will be cited in this review may ultimately find either greater support or be left without replication within the context of this very large dataset. However it is especially important to remember that the lack of evidence of an association in this European and Asian cohort may not eliminate the possibility of association in specific ethnic or geographically isolated groups.

1.2 Rare variants in AMD

The most recent efforts in AMD genetics research are now turning to the analysis of rare variants that may have strong implications in AMD pathogenesis. As noted above, the recent report of a rare variant that has been associated with hemolytic uremia and has been found in nonsyndromic cases of AMD would support such efforts, but a great deal more work will be needed to establish the extent to which these rare variants may account for the unexplained genetic contribution for AMD. One major challenge confronting this effort will be how to prove the causality of such rare variants since, by definition, a case-control approach would either have to be massive or would be incapable of providing statistical support of an association without a functional argument to group variants together. There is also the issue that with discovery of rare variants in novel AMD susceptibility genes, one has to consider if the associated phenotype is really a form of AMD or another distinct condition. Boone et al (Boon et al., 2009) found a high number of *PRPH2* mutations in a group of patients in the Netherlands with central areolar choroidal dystrophy that can be confused with AMD in elderly individuals. A similar situation arose previously in a large association study relating mutations in the *ABCA4* gene to AMD.(Allikmets et al., 1997) There has been considerable debate as to whether this finding was the result of a misclassification of a small group of Stargardt patients (with late onset of disease) as having AMD or if we should consider this a

form of genetic heterogeneity for AMD. These distinctions may change as we develop new technologies to distinguish phenotypic features of AMD-related disease.

A majority of the loci reported by multiple family-based linkage studies may be attributable to variants in specific genes that have now been found by candidate gene or genome-wide association studies. (Fisher et al., 2005) (see Table 1)

However formal testing of associations of these variants with family-based linkage studies has only been done in a few cases.(Jakobsdottir et al., 2008; Jakobsdottir et al., 2005) For the remaining linkage loci that have been reported in one or more family-based studies, one can argue that it is possible that some of the family-based linkage loci that have not been associated with AMD in case-control association studies are simply false-positive signals while other linkage-based loci represent real AMD genetic loci resulting from a sufficient number of rare highly –penetrant variants in those genes to generate a linkage signal but not be detectable using common SNPs in a case-control association design. The question remains whether rare variants in genes that have common variants associated with AMD, such as *CFH* and other genes in the alternative complement pathway, play a major role in AMD as well as the more challenging situation of rare variants in loci that have been identified in family-based linkage studies but do not reside in any known genes. New methods such as exome sequencing and exome chips, in conjunction with new analytical approaches for the testing of combined effects of multiple rare variants in a gene, may offer another window into this, as yet, unresolved genetic contributions to AMD.

Epistatic effects may also play a role in AMD genetics and consequently mask our ability to detect associations in some case-control cohorts or in family-based linkage or association studies. There are reports of interactions of smoking with genetic loci in AMD risk (Ayala-Haedo et al., 2010; DeAngelis et al., 2007; Nakanishi et al., 2010; Schmidt et al., 2006) and the potential for Vitamin D metabolism genes to modify risk.(Morrison et al., 2011; Parekh et al., 2007; Seddon et al., 2011) However not all studies have confirmed the smoking – gene interaction. Identifying these effects and the associated genes will be an iterative process as the biology of AMD pathogenesis unfolds.

2.0 Nontraditional Genetics of AMD

New technologies are leading to a growing appreciation of the potential for genomic rearrangements, expanding roles of non-transcribed DNA to modify and/or regulate gene expression, regulation and impact of alternatively spliced RNA transcripts, copy number variants, the roles of micro RNA and other non-translated RNA transcripts and epigenetics on the risk and pathogenesis of AMD. To date, we already have identified a number of insertions and deletions that may affect genes that have been implicated in AMD (see the work on the Complement factor H locus and *CFH*-related genes (Hughes et al., 2006; Kubista et al., 2011; Raychaudhuri et al., 2010; Schmid-Kubista et al., 2009; Spencer et al., 2008) and the *ARMS2* transcript (Wang et al., 2010)). We know that many of the SNPs that have been identified within GWAS are not within coding regions. While many of these informative SNPs may represent variants in linkage disequilibrium with some other causal variants, methods are being developed to determine if some of these noncoding SNPs are crucial in either the transcription of the transcript, the formation of an alternatively spliced transcript or even a shift in the distribution of multiple, spliced forms of a transcript from the same gene. Copy number variants are being explored for AMD-related genes (Liu et al., 2011; Meyer et al., 2011) and are being analyzed to determine how copy number variants play a role in this disorder. MicroRNAs have been implicated in AMD based on their ability to regulate angiogenesis(Zhou et al., 2011) and their potential role in inflammation.(Kutty et al., 2010) More recently Kaneko et al has suggested DICER1, a microRNA processing

enzyme, as a secondary role in the degradation of Alu RNA in the human RPE. In the absence of normal DICER1 activity, the accumulation of Alu RNA in the cell will induce cytotoxicity and result in RPE degeneration in mice. (Kaneko et al., 2011) This observation suggests another novel pathway of potential RPE atrophy that may be related to dry AMD. There is also the potential for epigenetic effects, modifications of DNA such as methylation, that may play a role in AMD pathogenesis.(Suuronen et al., 2007) This area of AMD genetics is in its infancy, in part because the methods have only recently become sufficiently robust to be used with the small samples obtained from eyes and we are gradually overcoming the limitations in obtaining sufficient numbers of human samples for genetic analyses.

3.0 Genetics of Disease Progression and Phenotype

Another current question is whether or not genetic variants that predict the occurrence of the disease will contribute differentially to the rate of progression and the phenotypes. While differences have been noted in the relative contributions of genetic variants to the development of either exudative or atrophic AMD(Farwick et al., 2010; Hayashi et al., 2010; Sobrin et al., 2011; Wegscheider et al., 2007) or the types of drusen (Boon et al., 2008; Grassi et al., 2007; Seddon et al., 2009b), there is no clear consensus or delineation of genetic variants that are predictive of progression to geographic atrophy or exudative AMD.

There have been recent reports of specific genotypes associated with specific AMD characteristics. Andreoli et al (Andreoli et al., 2009) conducted a fairly comprehensive survey regarding known AMD-related genetic variants to multiple phenotypic aspects of AMD, including age at diagnosis, visual acuity and clinical features of AMD. They found associations between SNPs within the *ARMS2* locus and several clinical features such as age of diagnosis, RPE hyperpigmentation with large drusen and poorer visual acuity but no such associations were noted for SNPs within the *CFH* locus. However, like in most associations, the separation of genotypes and phenotypes into distinct groups was not observed. At best, these results suggest that different genetic backgrounds may influence the likelihood that a person will have a specific characteristic of the AMD phenotype (including age of onset and rate of progression) but that one can't use a genetic profile to predict the natural history of a person's AMD experience. Smith et al (Smith et al., 2011) reported an association of macular reticular drusen with the AMD-associated risk allele of rs10490924 in *ARMS2* and a negative association with the AMD-associated risk allele of rs1061170 in the *CFH* gene. Previously, one group had reported that basal laminar drusen appeared to be associated with compound heterozygous variants in the *CFH* gene (affected individuals had one allele with the Y402H variant and the other CFH allele had either a nonsense, missense, or splice variant.(Boon et al., 2008) Seddon et al (Seddon et al., 2009b) reported an association of peripheral reticular degeneration of the pigment epithelium and extramacular drusen with AMD-associated risk alleles in *CFH*, but not with those of *ARMS2*. However in this study, these retinal peripheral findings were reported solely from clinical examinations and not photographically documented, which raises concerns about completeness and accuracy of detection. The implications of these different phenotypes on the progression of AMD and the responses to therapy are still unknown.

While many investigators and clinicians believe that genetics must underlie the determination of whether an individual will develop soft drusen or basal laminar drusen or go on to develop geographic atrophy or a choroidal neovascular AMD, one should appreciate that even for the Mendelian monogenic disorders, we still lack a basic understanding for genetic and epigenetic causes of variable expressivity and pleomorphism, even within families whose affected members share the same primary mutations.

Genetic studies have drawn into question whether or not polypoidal choroidopathy (PCP) is a distinct entity from AMD or simply an alternative phenotype underlying a common pathway of causality.(Fuse et al., 2011; Gotoh et al., 2010; Hayashi et al., 2010; Lima et al., 2010; Nakanishi et al., 2010; Tanaka et al., 2011; Zhang et al., 2011) Recently, there have been reports of genetic variants that are associated with PCP but do not appear to be related to AMD.(Zhang et al., 2011) Similarly there is one report of a SNP in the elastin gene that is associated with AMD in the Japanese population that is not associated with PCP in the same cohort.(Yamashiro et al., 2011) It should be noted that in multiple Caucasian cohorts, no variants in the elastin gene have been found to be associated with AMD. (Chen et al., 2010a; Kopplin et al., 2010; Neale et al., 2010) However because different ethnic groups have strikingly disparate prevalences of AMD and PCP, the presence or lack of some association with specific SNPs may be more reflective of difference in haplotype frequencies, different causative variants and/or epistatic effects that can occur with different genetic backgrounds. (Hu et al., 2011)

4.0 Biomarkers for AMD – a surrogate for genetic DNA variants?

Due to the implication of the inflammatory and alternative complement pathways in AMD pathogenesis, a number of groups have explored the relevance of serum-based protein markers of inflammation to predict AMD. These include C-reactive protein (Kim et al., 2008; Robman et al., 2010; Seddon et al., 2010), complement factors (Reynolds et al., 2009; Scholl et al., 2008), circulating VEGF (Haas et al., 2011), apolipoprotein B (Fauser et al., 2011), anti-retinal antibodies (Kubicka-Trzaska et al., 2011) lipid levels (Reynolds et al., 2010), carboxyethylpyrrole (CEP) antibodies (Gu et al., 2010; Gu et al., 2003), and Vitamin D (Parekh et al., 2007; Seddon et al., 2011). Several positive associations have been reported. However, it is unclear if these biomarkers reflect only the current state of AMD-related disease. Are these biomarkers actually reflective of a causal role such that therapies intended to modulate the serum levels of these proteins would have a beneficial impact on AMD progression? There is evidence that combined predictive models for AMD that include diet, smoking, exogenous risk factors, family history, genetic variants and clinical findings can provide insights into the likelihood of progression of advanced disease.(Feigl and Morris, 2011; Jakobsdottir et al., 2009; Reynolds et al., 2009; Seddon et al., 2009a; Seddon et al., 2011) However, currently there is no evidence that the measurement of biomarkers in the serum of a clinically normal and asymptomatic individual can be used as an effective predictor for the development of AMD or likelihood of disease progression. Visual function (reduced mesopic vision) and retinal structure precursors of AMD have been proposed (Feigl et al., 2011) as early biomarkers for AMD based on their association with high-risk genotype profiles in the absence of clinical manifestations of AMD, but whether these can be replicated in larger, more prospective studies needs further investigation.

Genetic variants are set at the time of conception and are constant throughout life, while biomarkers can reflect the dynamic combination of genetic, epigenetic, environmental and dietary factors that define an individual’s vulnerability to disease. Biomarkers, whether they are serum proteins or abnormalities detected by visual function testing or retinal anatomy, are particularly important in AMD because of the possibility that they might be used to monitor the effectiveness of preventive or therapeutic interventions prior to the development of the AMD findings in the eye. Just as many clinicians use serum cholesterol levels to calculate risk of atherosclerotic disease and to monitor the body’s response to dietary changes or medications, so do we seek similar biomarkers for AMD. However we face the same controversies and challenges that confront the rest of medicine, as we attempt to show that long-term modification of a biomarker by a controlled intervention will actually have a beneficial impact on the later development of the disease itself. We have to consider the possibility that some biomarkers may be able to serve in this capacity, while others may be

more effective and appropriate for monitoring the effectiveness of therapy (such as the use of HbA1c to monitor the effectiveness of blood sugar control in diabetics).

5.0 Genetics-based Causality of AMD

Throughout the field of molecular genetics, there is a general consensus as to the criteria by which one establishes whether one or more mutations in a gene as causal (necessary and sufficient) to be responsible for a Mendelian (monogenic) disorder. These criteria include the segregation of the mutation between affected and unaffected family members, the consistency of finding different mutations in the same gene for independent cases, the lack of the mutation in the general population, and evidence of the functional impact of the mutation on either the expression or processing of the gene transcript or the structural and/or functional integrity of the encoded protein. There are similar criteria to address the statistical significance of an association of a variant with a complex genetic disorder including an appropriate correction for multiple testing and replication in an independent cohort. However, in many instances, the common variants that have been associated with AMD are not clearly affecting the function of a gene and/or its protein and, perhaps more importantly, the human genetic studies can't discriminate between the effect of the informative variant and other alterations in the genetic region that are in linkage disequilibrium with that variant. Establishing a genetics-based causality for a gene involved in a complex genetic disorder, particularly when the definition of causality is not based on "sufficient and necessary" but is probabilistic, is an ongoing challenge. As we are now observing in the field of AMD genetics, this challenge must be addressed by a combination of genomic exploration and strategies and methods that includes bioinformatics, biochemistry, cell biology and genetically manipulated animal models. This next section considers how the composite of molecular genetic studies for AMD have contributed to this issue of causality and the work that remains to be done.

5.1 Alternative Complement Pathway

The alternative complement pathway is a key part of the innate immune response pathway that is essential for the body to fight infection and to mount a suitable inflammatory response to a number of toxic compounds or infectious agents. There is compelling genetic evidence that the alternative complement pathway plays a key role in the causality of AMD. This conclusion is not based on a particular variant in a single gene, but rather the composite impact of a number of genetic variants that encode proteins for this pathway that contribute either positively or negatively to the risk of developing AMD (see Table 2).(Anderson et al., 2010)

Complement factor H is a negative regulator in the alternative complement pathway.(Clark et al., 2010; Lauer et al., 2011; Ormsby et al., 2008) However, there continues to be ongoing controversy as to what variants in the CFH locus are actually responsible for the altered functions that lead to either increased or decreased risk of developing AMD. The Y402H variant was originally reported as the common SNP strongly associated with AMD and considerable efforts have been expended to determine its functional consequences on the actions of complement factor H. For example, Weissman et al (Weismann et al., 2011) has reported that the Y402H variant specifically affects the ability of complement factor H protein to bind malondialdehyde a common lipid peroxidation product that has been implicated in AMD. However this CFH variant is in strong linkage disequilibrium with a number of markers in the region (Martinez-Barricarte et al., 2012) and more recent case-control association studies have indicated that there are high-AMD risk haplotypes covering the CFH locus that do not contain the Y402H variant.

Deletions and copy number variations in Complement factor H-related genes, CFHR1 and CFHR3 and CFHR5, have been reported within high-risk haplotypes for AMD. (Abarrategui-Garrido et al., 2009; Fritsche et al., 2010; Hageman et al., 2006; Hughes et al., 2006; Narendra et al., 2009; Schmid-Kubista et al., 2009{Kubista, 2011 #5464; Spencer et al., 2008)} Alterations in adjacent, complement factor-related genes could be responsible for the associations. Case-control association comparisons in larger cohorts offer one approach to identify the effects of low prevalence haplotypes that could shed light on causality, but one has to consider that rare variants within these haplotypes could be playing a confounding role. The challenge is how to determine the impact of these mutations in CFH and adjacent genes in the absence of evidence from animal model that truly replicate this multifaceted disease.

A number of other genes within the alternative complement pathway have been shown to have common variants that are strongly associated with AMD risk (protective and nonprotective). These include the complement factor genes, CFI, C3, the C2/CFB locus, and C7.(Dinu et al., 2007) No associations have been reported for complement factor D(Zeng et al., 2010) and conflicting results for the SERPING1-AMD association have been reported in larger case-control studies failing to confirm the initial report of a positive association. (Ennis et al., 2008; Klaver and Bergen, 2008; Kralovicova and Vorechovsky, 2009; Lee et al., 2010; Lu et al., 2010; Park et al., 2009)

5.2 Innate immune response pathway - Toll receptors and Chemotactic Cytokines

Given the clear evidence of the involvement of alternative complement pathway in AMD pathogenesis, it is reasonable to consider other players in the innate immune response as having common or rare variants that can contribute to AMD risk. The toll-like receptors (TLR) have been implicated in AMD by a few studies. There are also multiple studies that have failed to replicate any major association with any of the TLR genes. There has been considerable interest in the TLR4 variants(Zareparsi et al., 2005), particularly with respect to atrophic AMD, but some efforts have failed to find a significant association (Cho et al., 2009; Despriet et al., 2008; Edwards et al., 2008) One study has shown a positive association for TLR3 specifically for geographic atrophy with protection conferred by the variant, rs3775291 which changes leucine 412 to a phenylalanine(Yang et al., 2008) but the association could not be replicated by Klein et al(Klein et al., 2010). Other studies also failed to find significant associations between TLR3 and any forms of AMD. (Allikmets et al., 2009; Cho et al., 2009; Edwards et al., 2008; Edwards et al., 2009; Sng et al., 2011) Recently, based on a meta analysis and biological studies, Zhou et al (Zhou et al., 2011) suggested that a particular TLR3 variant, C1234T, reduces its protein activity and shows a protective effect on AMD. This is not the same variant used in the other TLR3 association studies. (Cho et al., 2009; Edwards et al., 2009; Klein et al., 2010; Kleinman et al., 2008; Lewin, 2009; Liew et al., 2009; Sng et al., 2011)

Chemokine (C-C motif) ligand 2 (CCL2) in Chromosome17q12 and it receptor, chemokine (C-C motif) receptor 2 (CCR2) in Chromosome 3p21.31 are important mediators of inflammation though their role as chemotactic cytokines that trigger both the migration and activation of leukocytes. Over 50 ligands bind to the G-protein-coupled chemokine receptors on the surface of leukocytes to regulate trafficking of these cells in response to innate and adaptive immune triggers. Knockout mice for these genes have been shown to manifest some AMD-like changes including drusen deposition and the development of choroidal neovascular membranes, thus it is reasonable to ask if there are AMD-related variants in these genes. However, to date, the results have been negative.(Chen et al., 2010a) Despriet, 2008 #4706} While some may interpret these negative results as a rationale for discounting the role of CCL2 and CCR2 in the human form of AMD, one must consider the limitations of case-control association studies and the possibility that a common functional variant in

either of these genes would be associated with serious immune deficiencies or autoimmune disorders.

5.3 Non- complement related genes involved with AMD

5.3.1 The 10q26 locus – ARMS2 versus HTRA1—The 10q26 locus was originally identified by family-based linkage analysis of affected sibpairs (Weeks et al., 2004) and later it was shown that this linkage signal could be accounted for by a common SNP in the region of a hypothetical transcript, LOC38776, which was in essentially complete linkage disequilibrium with two adjacent genes, PLEKH1 and HTRA1.(Jakobsdottir et al., 2005; Rivera et al., 2005) Case-control association studies confirmed the impact of this locus on non-familial AMD risk (Tong et al., 2010) and virtually every ethnic population has shown consistent associations of this locus with AMD. The ARMS2 locus has been reported to have interactions with RAR-related orphan receptor A (RORA), a receptor involved in cholesterol transport and also associated with AMD.(Schaumberg et al., 2010; Silveira et al., 2010). The ARMS2 locus has also be reported to have interactions with an inverse effect of hormone replacement therapy on AMD (Edwards et al., 2010). However, there is controversy as to whether the ARMS2 transcript or the HTRA1 transcript is responsible for the AMD risk conveyed by the 10q26 locus.

Biological evidence has also been sought to elucidate the etiology of the 10q26 locus on AMD. In support of the hypothesis that the ARMS2 transcript is responsible for the association of this locus with AMD, investigators have established that the encoded mRNA and corresponding peptide is expressed in the retina (though it is disputed whether or not the ARMS2 protein is associated with mitochondria or the cytosol (Kanda et al., 2007; Wang et al., 2009a). More recently, the ARMS2 protein has been described as a constituent of the extracellular matrix and may interact with Fibulin-6 (Kortvely et al., 2010) and that the mRNA has a unique splice form in the retina that is not common in other tissues.(Wang et al., 2012) Detractors have noted that the transcript is only found in primates, that localization studies of the protein have been confusing and contradictory, and that no function has been established for the protein encoded by this transcript.(Stanton et al., 2012) Without an animal model that can be genetically manipulated and also expresses this transcript, it is difficult to conduct studies of its biology.

In contrast, HTRA1 has been shown to be easily detectable in the retina with higher concentrations in the central macula. Overexpression of HTRA1 causes alterations in the elastic layer of Bruchs membrane (Vierkotten et al., 2011) and, as a serine protease, appears to cleave a number of proteins that regulate both the alternative complement pathway and amyloid deposition.(An et al., 2010) A useful review of this controversy has recently been published.(Stanton et al., 2012)

To a lesser extent than the ARMS2/HTRA1 controversy, there are other instances in which SNPs have been found to be associated with one or more forms of AMD and which are located in regions of linkage disequilibrium that cover two or more candidate genes. This has been true for the C2/CFB locus, which also extends to include the SKIV2L gene, for which an intronic SNP has been reported to be protective for three distinctive haplotypes. (Kopplin et al., 2010) It is not yet clear if this protective association can be attributed independently to this gene, located within the class III region of the major histocompatibility complex and which encodes a DEAD box protein with unknown function in the eye. As one considers the most recent genome-wide association studies for AMD, there are other instances in which multiple genes are potential candidates in the vicinity of one or more informative SNPs.

5.3.2 Genes and pathways implicated in AMD—Unlike the ARMS2/HTRA1 controversy in which we are dealing with at least one gene for which no known function is known, most of the other genes implicated by AMD genetic studies have a known or suspected role in the retina. Whether or not these "known" roles are the ones that make them relevant to AMD pathogenesis is not clear. There are many examples of proteins playing multiple roles in the body, in some cases serving structural, signaling and/or enzymatic roles. We can use pathway analyses to strengthen the case for the mechanisms of action when multiple genes within the same pathway are implicated in AMD, such as for the alternative complement pathway, as long as we recognize the current limitations of our current understanding of these complex and interconnected processes. There are recent efforts to use genetic analyses to identify how genetic variants affecting different pathways might alter the rate of progression or severity of AMD (Yu et al., 2012), but such efforts are constrained by the numbers of AMD-affected individuals within genetic studies who are being followed in a prospective manner.

5.3.2.1 Basement membrane and extracellular matrix genes: There is a wealth or research that has emphasized the maintenance of the basement membrane and the extracellular matrix as a contributing factor in AMD. In addition to histopathologic studies of AMD eyes, we have evidence of multiple genes whose gene products are critical to the structure and maintenance of the extracellular matrix and basement membrane. Some of these have been reported to have variants that are associated with the risk of AMD. Some of these associations have been replicated while others have not. Table 3 summarizes these genes that have been implicated in AMD and/or juvenile macular dystrophies. The last entry that is marked with an "*" has only been recently discovered by the AMD gene consortium to have an association with AMD and, like other examples encountered in this field, the informative SNP is in close proximity to two candidate genes, COL15A1 and TGFBR1. [AMD consortium]

5.3.2.2 Lipid-related genes: The first genetic variant that was demonstrated for AMD was in the *ApoE* gene. The role of lipid metabolism has been long recognized as a potential factor in AMD pathogenesis given the changes in the RPE and Bruch's membrane and because the lipid metabolic pathway also plays a critical role in the transport and metabolism of the retinoids and carotenoids (see reviews by Mettu, Sparrow, Jarrett, Bhutto, Handa). More recent studies demonstrating multiple interactions of lipid metabolism and the inflammatory pathways have created additional concepts as to how these processes may be interrelated in AMD pathogenesis. While some of the lipid metabolism genes that have been implicated in AMD associations may eventually fail to be replicated, as one can see from Table 4, there is an aggregate body of evidence that makes a compelling case that the lipid metabolism pathway is a key element in AMD. The challenge in the coming years will be to decipher the mechanisms and connections of lipid biology that provide a reasonable basis for understanding AMD and finding useful targets for reducing risk and/or slowing disease progression.

5.3.2.3 Mitochondrial genetics: Oxidative stress and lipid peroxidation have long been thought to play a role in AMD pathogenesis and thus there has been critical interest in the potential role of variants associated with nuclear genes that encode mitochondrial proteins as well as for those genes that are contained within the mitochondrial genome (see review by Jarrett). Damage to the mitochondrial genome in the RPE has been associated with aging and AMD severity (Lin et al., 2011; Wang et al., 2008a) and more extensive genetic alterations in the mitochondria of AMD patients has been observed.(Kenney et al., 2010) There has been only limited data regarding nuclear genes that are related to oxidative stress. There was an early report of an association of a polymorphism in Paraoxonase 1 (*PON1*)

with AMD and later Ikeda et al(Ikeda et al., 2001) reported a protective variant GLN192Arg for wet AMD. A more recent case-control study by Baird et al. failed to replicate the prior protective association or establish an association of *PON1* variants with AMD.(Baird et al., 2004) A more recent and larger study has shown a weak association of the *PON1* Leu55Met variant with an increased risk of exudative AMD and a protective effect of the Gln192Arg variant.(Pauer et al., 2010) Two studies have evaluated variants in *SOD2*, superoxide dismutase-2 with respect to AMD and found no association.(Brion et al., 2011; Kondo et al., 2009) Mitochondrial genetics for AMD can be divided into those studies that have reported an association with a specific genetic variant, such as *MTND2*LHON4917G* (Canter et al., 2008) and those who have evaluated mitochondrial haplotypes for associations with advanced AMD (Jones et al., 2007; SanGiovanni et al., 2009; Udar et al., 2009)

5.3.2.4 Vitamin D pathway genes: There have been several studies suggesting an association of Vitamin D levels with the prevalent risk of AMD.(Millen et al., 2011; Parekh et al., 2007) To date, only one study has evaluated variants with those genes known to encode enzymes that are responsible for processing Vitamin D. These genes include the vitamin D receptor [*VDR*]; cytochrome P450, family 27, subfamily B, polypeptide 1 [*CYP27B1*]; cytochrome P450, family 24, subfamily A, polypeptide 1 [*CYP24A1*]; and *CYP27A1*. Using a family-based cohort of 481 siblings and then a replication set of individuals from another family cohort and two case-control cohorts comprising 2,528 individuals, SNPs in *CYP24A1* were demonstrated to influence AMD risk after controlling for other known genetic and exposure risk factors.(Morrison et al., 2011) The authors noted that all of the genes that were investigated in this candidate gene study of the Vitamin D metabolic pathway have been mapped within regions that have previously been shown to have linkage to AMD in family-based linkage analyses (Seddon et al., 2003), though no analyses were done to establish that the variants in *CYP27A1* were able to account for the observed linkage signal. The observed overlap could be coincidental, but could also reflect the potential of rare variants in one or more of these genes to have an impact on AMD risk.

5.3.2.5 Angiogenesis-related genes: Angiogenesis clearly plays a major role in the development of choroidal neovascularization that are the hallmark of exudative AMD. There has been a particular interest in genes that regulate this process as a means to better understand the likelihood of progression to the exudative form of AMD as well as their responses to anti-angiogenic therapies such as anti-VEGF medications that are now in widespread use. The candidate genes for analysis have included the four forms of vascular endothelial growth factor, *VEGF* (also known as *VEGF-A*) in Chromosome 6p21.1 and *VEGF-B* in Chromosome 11q13.1) *VEGF-C* in Chromosome 4q34.3 and *VEGF-D* (also known as *FIGF*) in Chromosome Xp22.2, the three isoforms of the vascular growth factor receptor (*VEGFR-1* (*Flt-1*) in Chromosome 13q12.3, *VEGFR-2* (*KDR/Flk-1*) in Chromosome 4q12, and *VEGFR-3* (*Flt-4*) in Chromosome 5q35.3, and hypoxia inducible factor 1 alpha (*HIF1* or *HIF1alpha*) in Chromosome 14q23.2.(Arjamaa et al., 2009) To date, no variants within HIF1, VEGFB, VEGFC or VEGFD have been reported to be associated with any subtypes, incidence, or prevalence of AMD.

The initial report of *VEGF* polymorphisms-exudative AMD association (Churchill et al., 2006) was not replicated in the larger case-control study by Richardson et al (Richardson et al., 2007) nor by Fang et al.(Fang et al., 2009) Both studies employed tag SNPs in the *VEGF* gene. In a smaller case-control study of Chinese population in Taiwan, Lin et al(Lin et al., 2008) found no association of a *VEGF* haplotype with AMD but observed a strong association of a functional SNP, *VEGF*+936 C/T, with exudative AMD. This particular SNP was not in strong LD with the other *VEGF* SNPs that were tested. In contrast, another small case-control study in a Chinese population using both functional and tag SNPs for *VEGF* failed to find an association with exudative AMD.(Qu et al., 2011) Another group (Immonen

et al., 2010) that employed tag SNPs for the *VEGF* gene, also failed to identify an association with exudative AMD. The Rotterdam Study (Boekhoorn et al., 2008) conducted a large population-based case-control study examining the associations of 3 common SNPs and haplotypes within the *VEGF* gene with incident early and late AMD and found no evidence for an association. This negative result, based upon a well-characterized and large number of cases and controls, has been difficult to reconcile with the positive associations for *VEGF*-related SNPs with both family-based and case control cohorts of advanced AMD(Haines et al., 2006) and the results of the Oregon group who looked at the progression of AMD from early to advanced forms and found evidence of an association with the VEGF gene.(Francis et al., 2009) Several recent large, collaborative case-control studies have provided compelling evidence of an association between *VEGF* and AMD risk.(Yu et al., 2011)[AMD gene consortium]. To date, only one study has found evidence of a weak association between a rare *VEGFR-2* haplotype and exudative AMD.(Fang et al., 2009) Finally, the most recent results from the AMD genetics consortium have implicated *COL15A1* (Chromosome 9q22.33) and/or *TGFBR1* (Chromosome 9q22.33) in AMD pathogenesis due to an informative, common SNP within the vicinity of both genes. While we do not know which gene (or possibly both) is biologically responsible for the observed association, both genes have been implicated in angiogenesis. *COL15A1* is in the same class of collagens as *COL18A1* that is cleaved to form the peptide, Endostatin, a potent inhibitor of angiogenesis. *TGFBR1* is a TGF receptor that is a member of the same signaling pathway for angiogenesis described by the Ingenuity Pathway Analysis tool (Ingenuity Systems, Redwood, CA) [see AMD gene consortium paper].

5.3.2.6 Iron metabolism genes: There has been considerable interest in the role of iron metabolism in the eye in general, and, specifically, with respect to AMD. A number of studies have documented changes in gene expression related to proteins that are critical in iron metabolic pathway in early and late AMD as well as the deposition of iron in the AMD-affected retinal pigment epithelium and basement membrane.(Chowers et al., 2006; Wong et al., 2007) To date, the genetic studies to establish a role of iron metabolism in AMD have been relatively weak. Nearly all of the recent studies of possible associations of transferrin and heme oxygenase-1 and -2 genes have come from a single group (Synowiec et al., 2011; Wysokinski et al., 2011a; Wysokinski et al., 2011b) and replication from larger cohorts has not been done. However, given the critical nature of iron metabolic pathways for the human body, one should not exclude the potential role of these genes in AMD.

5.3.3 AMD – associated genes of unclear significance—The genes listed in Table 5 have been implicated by either family-based or case-control association studies. For most of them, their potential role in AMD pathogenesis is still uncertain, partly because they are implicated by proximity with respect to a common SNP that is associated with one or more forms of AMD. For some, like *MYRIP* and *ADAMTS9*, one can make plausible arguments based on the known functions of the genes to strengthen their roles as AMD candidate genes. For the others, the evidence is less certain and more biological as well as genetic studies will be required.

6.0 The ocular-specific “trigger” for AMD

Nearly all of the genes that have been implicated in the risk for developing AMD do not have eye-specific expression patterns. The RPE strongly expresses many of the genes that encode regulators of the alternative complement pathway but there have been reports that systemic levels of complement factors may play a major role in the process. In the mean time, we know that drusen, which are hallmarks of AMD phenotype contain many other constituents such as beta amyloid (Ding et al., 2011; Kurji et al., 2010; Luibl et al., 2006; Wang et al., 2008b; Wang et al., 2009b) and alpha synuclein (Klegeris and McGeer, 2007;

Okamoto et al., 2010) that are present in other deposits in the body in association with atherosclerosis and Alzheimer disease. At the same time, the epidemiologic evidence for a relationship among Alzheimer Disease, atherosclerosis and AMD has been relatively weak. (Roca-Santiago et al., 2006; Vingerling et al., 1995) Thus we are left with the question as to what is the basis of the tissue specificity of AMD, which results in these shared pathologic pathways resulting in an eye-specific disorder.] To date, the tissue-specific trigger for AMD pathogenesis in the eye is still unknown and is the subject of considerable study and conjecture (see Sparrow, see Handa).(Ref in journal) Unfortunately, the current genetic studies that have been done with human populations have not yielded any answers. The genes and pathways implicated in the molecular genetic studies provide key players in the process and potential targets for AMD pathogenesis, but until we understand this key issue, the puzzle will remain incomplete.

7.0 Genetic diagnostics for AMD

Several companies are now offering clinical services for those who wish to have a genetic estimate of their AMD risk. While there is strong evidence that those with the highest aggregation of high-risk variants are highly likely to develop AMD while those with the lowest aggregation of risk variants have a very low rate of developing AMD (Chen et al., 2010a; Seddon et al., 2009a; Spencer et al., 2011), the current genetic models tend to lack the level of sensitivity and specificity that one would normally demand of a clinical test. (Jakobsdottir et al., 2009) The majority of individuals in the population are somewhere in the middle range of AMD risk and the predictive benefits of molecular diagnostic testing is low and potentially misleading. Most predictive models are based on comparing those with disease (usually advanced AMD) with controls (Gibson et al., 2010; Jakobsdottir et al., 2008; Schaumberg et al., 2007; Seddon et al., 2008, 2009a)) rather than prospectively assessing the incidence of disease in an aging population. Some recent efforts have attempted to improve the predictive modeling by considering exogenous factors such as smoking and diet, as well as clinical features of the retina, (Chen et al., 2011; Hughes et al., 2007; Seddon et al., 2011; Spencer et al., 2011) but validation of these models in a young, at-risk population has not yet been established.

At present, there is no therapeutic intervention that can lower the risk of AMD incidence other than the relatively modest benefits suggested for the avoidance of smoking, intake of low glycemic index diet, an increased uptake of carotenoids (lutein and zeaxanthin), vitamin D (sufficient to avoid deficiency). However there is recent evidence that dietary interventions such as antioxidants, EPA/DHA, lutein/zeaxanthin and zinc can specifically reduce the impact of an individual’s underlying genetic risk for developing AMD.(Ho et al., 2011)

A number of clinicians have argued that genetic testing for AMD risk would provide additional motivation for patients to adhere to preventive measures. However, while such an approach might be effective for high-risk individuals, an intermediate or low genetic risk profile could act as a disincentive for the adoption of preventive measures. In addition, in the absence of disease, the knowledge of a high genetic risk for AMD can create anxiety and negatively impact quality of life in individuals as well as create guilt for those who develop disease having not adhered to the recommendations while creating disillusionment and anger in those who assiduously adhered to the risk-lowering measures and yet still developed the disease. Most clinicians who lack training of genetic counseling are not prepared to deal with the results of genetic testing and thus one has to approach such testing with a reasonable level of caution.

Genetic testing and risk prediction for AMD becomes more justifiable if there is a preventive therapy that involves an intervention that goes beyond good health practices (no smoking, balanced diet, exercise, reasonable nutrient supplements) and entails an element of risk or cost that makes it worthwhile to limit those treatments to only those with increased risk. The challenge will be to find the optimal risk-benefit point along the AMD-risk profile for every given age so that one can decide which individuals should receive those treatments and at what age to start the intervention (which presumably would be ongoing for the rest the person's life). To date, no such age-dependent risk-benefit model has been developed based solely on a genetic risk model for any disease, though some efforts have been made in trying to decide when to intervene in breast cancer for people with *BRCA1* or *BRCA2* mutations. Given the exogenous factors that may contribute to AMD risk, as well as the uncertainties as to how to quantitate the risks and benefits of a therapy that has not yet been developed, this could prove highly elusive. It is unlikely that a monotherapy will be equally effective in preventing the manifestations of a complex genetic disorder among a genetically diverse group. It is also reasonable to expect that the potential side effects of any such monotherapy will also be affected by an individual's personal genetic profile. We are coming to realize that even compounds such as vitamins may have adverse effects on some disease risks while lessening the risk for other conditions. As a result of these complexities, as well as the fact that multiple disease-risks are age-dependent, a medication may only be appropriate for those with the highest risk of developing AMD starting at age 40, and might or might not be appropriate in patients with moderate risk and early retinal changes at age 65 or 70. If one can show that some genetic variants can determine the risk of developing the side effects or complications of the medication, then this could also be integrated into the decision-making process. This approach represents the "dream" of personalized medicine, but the reality of implementing this in an evidence-based fashion will be challenging without enormous cohorts and a willingness of the health care system to allow such strategies to be tested for the general population and then subsequently refined. It should be appreciated that using genetic (and nongenetic) risk factors to identify high-risk cohorts could have an immediate benefit in reducing the size and duration of AMD-related clinical trials.(Seddon et al., 2011)

Many clinicians already use a combination of clinical features (such as early onset of drusen with high risk characteristics or numbers) and a family history of AMD to identify individuals for whom life style modifications and AREDS supplements are recommended. However the effectiveness of such interventions and their timing remain untested.

There is clearly a desire to use our knowledge about the causality of AMD that has been inferred from genetic studies to identify new targets for therapy. This has been the driving force in the use of complement inhibitors to alter the course of AMD. As additional pathways are defined as playing a role in the etiology of AMD, new potential targets for therapy will be identified and pharmacologic interventions will be developed.

8.0 Pharmacogenetics and Genetics-based therapeutics for AMD

There is also considerable interest in using genetic testing as a means of predicting the likelihood that a person will respond favorably (or unfavorably) to therapy. Several small scale studies have been done, (Shastry, 2010) (Bessho et al., 2011; Kloeckener-Gruissem et al., 2011; Teper et al., 2010), but this approach has limited benefits at this time, since a relative difference in response to therapy associated with genotypes would not be clinically relevant to the choice of existing treatments and when to switch from one therapy to an alternative. The most effective current treatments for exudative AMD are anti-VEGF medications that all work via the same mechanism. There have been several attempts to identify genetic variants associated with response to anti-VEGF therapy. One group

(Immonen et al., 2010) using tag SNPs for the *VEGF* gene, failed to identify an association with exudative AMD and yet they found two *VEGF* SNPs that were significantly associated with the response of patients to photodynamic therapy (PDT) using Vertiporfin and infrared laser) for choroidal neovascularization. A subsequent study also looked at the role of *VEGF* variants with respect to the response to PDT therapy in a Japanese cohort, and did not find any association, though they did observe a relationship of *HTRA1* and *CFH* variants with PDT responders.(Tsuchihashi et al., 2011) Similarly a study of treatment response to intravitreal anti-VEGF therapy (ranibizumab) in a Swiss cohort (Kloeckener-Gruissem et al., 2011) also failed to find associations with *VEGF* polymorphisms though *CFH* and *FZD4* alleles appeared to collectively impact the treatment outcome. However these initial studies do not provide compelling evidence that there are genetic variants or a genetic profile that would alter the preference of one medication in this class of drugs as compared to another for a given individual. At this time, there is no genetic rationale for determining or modifying one's choice of therapy for exudative AMD for an individual, regardless of their genetic risk profile. Every therapy has a certain percentage of treatment failures and one might consider using a patient's genetic profile to guide when one would switch to an alternative, combined therapy, but given that none of the current studies have shown such dramatic differences based on genetic risk profiles, there would be little justification for such actions. See: Parmeggia et al and Nakata el al(Nakata et al., 2011; Parmeggiani et al., 2011)

The dream of every AMD geneticist is that one or more of the genes that have been identified from family-based or case-control association studies will prove to be a suitable target for a definitive therapy to block the development of AMD or to arrest its progression. However as we learn more about this complex genetic disorder, many of us are coming to realize that, with the exception of a relatively small number of individuals and families who develop their AMD as a result of a highly penetrant and rare genetic variant (such as the one described recently by xx et al for *CFH*), we cannot view the treatment of AMD in the same fashion that we would think of a monogenic disorder in which a single genetic lesion is causative of disease. To date, the effects of the multiple genes that have been implicated in AMD incidence and/or progression act predominantly in an additive fashion suggesting that each genetic variant contributes independently to the overall risk to the individual. In practical terms, we do not know if the future therapy for AMD will be multifactorial and potentially involve a combination of diet, lifestyle and pharmacologic interventions or if we will be able to have a major impact on the condition, despite its diverse genetic and non-genetic contributors, by acting upon a single pathway. The situation may ultimately be like the treatment of essential hypertension, with a variety of therapies that have variable efficacies for different individuals. Today, we use an empiric approach towards the treatment of essential hypertension, offering the patient one of several standard medications and a prescription for lifestyle and dietary changes and then we add or modify those medications based on a clinical response. Only in rare cases, do we employ genetic testing of an individual to customize their hypertensive treatment. In contrast, for AMD we don't have the appropriate biomarkers to monitor a person's response to any AMD preventive therapy. We are still developing the tools for accurate quantitation of the AMD phenotype when the person has clinical findings in order to monitor disease progression. There is no clinical equivalent of a blood pressure measurement to assess a person's response to an AMD-related preventative therapy. In contrast, we do have such clinical tools for assessing a person's response of their exudative AMD to intravitreal anti-VEGF therapies.

The technologies for sequencing the entire exome of an individual and even their entire genome are rapidly approaching a level of cost and availability so as to be feasible in clinical practice. However, unless we establish a means of incorporating all of the potential rare and private genetic variants that can contribute to AMD risk with the common variants

that we have already discovered, our ability to use molecular genetics predictive testing for AMD will be limited to those who are at the extreme poles of risk based on the common variants and we will miss those rare cases whose AMD (or AMD-like) disease is arising from a rare mutation. The solution to this dilemma may rest in the combination of the common genetic variants and clinical biomarkers (which may include early retinal changes as well as serum proteomics and metabolomics) that may allow us to better discriminate those with intermediate levels of AMD genetic risk who will be likely to develop vision-threatening AMD from those who will simply accumulate a few drusen. The sensitivity of these dynamic biomarkers during the course of a person's lifetime as well as the costs, risks and benefits of the potential therapies will determine at what stage we can reasonably intervene to alter the course of this disease. Molecular geneticists, through family-based linkage and association studies and by case-control association studies, can take credit for having brought a revolutionary degree of understanding and direction to the work on AMD that continues to be driven by the clinicians and researchers in all of the life and basic sciences. Even as we move forward with the newest genetic analytical methods and genomic technologies, we will be integrating these efforts with all of the modern research strategies and methods to both make sense of the discoveries during this past decade and to find the path towards bringing this knowledge into the realm of clinical practice so that we can protect the vision of our elderly population throughout the rest of their lives.

Acknowledgments

This work was made possible by the support from NEI R01-EY09859, Harold and Pauline Price Foundation, and Research to Prevent Blindness.

References

Abarrategui-Garrido C, Martinez-Barricarte R, Lopez-Trascasa M, de Cordoba SR, Sanchez-Corral P. Characterization of complement factor H-related (CFHR) proteins in plasma reveals novel genetic variations of CFHR1 associated with atypical hemolytic uremic syndrome. Blood. 2009; 114(19): 4261–4271. [PubMed: 19745068]

Abecasis GR, Yashar BM, Zhao Y, Ghiasvand NM, Zareparsi S, Branham KE, Reddick AC, Trager EH, Yoshida S, Bahling J, Filippova E, Elner S, Johnson MW, Vine AK, Sieving PA, Jacobson SG, Richards JE, Swaroop A. Age-related macular degeneration: a high-resolution genome scan for susceptibility loci in a population enriched for late-stage disease. Am J Hum Genet. 2004; 74(3): 482–494. [PubMed: 14968411]

Allikmets R, Bergen AA, Dean M, Guymer RH, Hageman GS, Klaver CC, Stefansson K, Weber BH. Geographic atrophy in age-related macular degeneration and TLR3. N Engl J Med. 2009; 360(21): 2252–2254. [PubMed: 19469038]

Allikmets R, Shroyer N, Singh N, Seddon J, Lewis R, Bernstein P, Peiffer A, Zabriskie N, Li Y, Hutchinson A, Dean M, Lupski J, Leppert M. Mutation of the Stargardt disease gene (ABCR) in age-related macular degeneration. Science. 1997; 277:1805–1807. [PubMed: 9295268]

An E, Sen S, Park SK, Gordish-Dressman H, Hathout Y. Identification of novel substrates for the serine protease HTRA1 in the human RPE secretome. Invest Ophthalmol Vis Sci. 2010; 51(7): 3379–3386. [PubMed: 20207970]

Anderson DH, Radeke MJ, Gallo NB, Chapin EA, Johnson PT, Curletti CR, Hancox LS, Hu J, Ebright JN, Malek G, Hauser MA, Rickman CB, Bok D, Hageman GS, Johnson LV. The pivotal role of the complement system in aging and age-related macular degeneration: hypothesis re-visited. Prog Retin Eye Res. 2010; 29(2):95–112. [PubMed: 19961953]

Andreoli MT, Morrison MA, Kim BJ, Chen L, Adams SM, Miller JW, DeAngelis MM, Kim IK. Comprehensive analysis of complement factor H and LOC387715/ARMS2/HTRA1 variants with respect to phenotype in advanced age-related macular degeneration. Am J Ophthalmol. 2009; 148(6):869–874. [PubMed: 19796758]

Arjamaa O, Nikinmaa M, Salminen A, Kaarniranta K. Regulatory role of HIF-1alpha in the pathogenesis of age-related macular degeneration (AMD). Ageing Res Rev. 2009; 8(4):349–358. [PubMed: 19589398]

Ayala-Haedo JA, Gallins PJ, Whitehead PL, Schwartz SG, Kovach JL, Postel EA, Agarwal A, Wang G, Haines JL, Pericak-Vance MA, Scott WK. Analysis of single nucleotide polymorphisms in the NOS2A gene and interaction with smoking in age-related macular degeneration. Ann Hum Genet. 2010; 74(3):195–201. [PubMed: 20374233]

Baird PN, Chu D, Guida E, Vu HT, Guymer R. Association of the M55L and Q192R paraoxonase gene polymorphisms with age-related macular degeneration. Am J Ophthalmol. 2004; 138(4):665–666. [PubMed: 15488805]

Barral S, Francis PJ, Schultz DW, Schain MB, Haynes C, Majewski J, Ott J, Acott T, Weleber RG, Klein ML. Expanded genome scan in extended families with age-related macular degeneration. Investigative Ophthalmology & Visual Science. 2006; 47(12):5453–5459. [PubMed: 17122136]

Bessho H, Honda S, Kondo N, Negi A. The association of age-related maculopathy susceptibility 2 polymorphisms with phenotype in typical neovascular age-related macular degeneration and polypoidal choroidal vasculopathy. Mol Vis. 2011; 17:977–982. [PubMed: 21541271]

Boekhoorn SS, Isaacs A, Uitterlinden AG, van Duijn CM, Hofman A, de Jong PT, Vingerling JR. Polymorphisms in the vascular endothelial growth factor gene and risk of age-related macular degeneration: the Rotterdam Study. Ophthalmology. 2008; 115(11):1899–1903. [PubMed: 18708255]

Boon CJ, Klevering BJ, Cremers FP, Zonneveld-Vrieling MN, Theelen T, Den Hollander AI, Hoyng CB. Central areolar choroidal dystrophy. Ophthalmology. 2009; 116(4):771–782. 782 e771. [PubMed: 19243827]

Boon CJ, Klevering BJ, Hoyng CB, Zonneveld-Vrieling MN, Nabuurs SB, Blokland E, Cremers FP, den Hollander AI. Basal laminar drusen caused by compound heterozygous variants in the CFH gene. Am J Hum Genet. 2008; 82(2):516–523. [PubMed: 18252232]

Brion M, Sanchez-Salorio M, Corton M, de la Fuente M, Pazos B, Othman M, Swaroop A, Abecasis G, Sobrino B, Carracedo A. Genetic association study of age-related macular degeneration in the Spanish population. Acta Ophthalmol. 2011; 89(1):e12–22. [PubMed: 21106043]

Canter JA, Olson LM, Spencer K, Schnetz-Boutaud N, Anderson B, Hauser MA, Schmidt S, Postel EA, Agarwal A, Pericak-Vance MA, Sternberg P Jr, Haines JL. Mitochondrial DNA polymorphism A4917G is independently associated with age-related macular degeneration. PLoS ONE. 2008; 3(5):e2091. [PubMed: 18461138]

Chen W, Stambolian D, Edwards AO, Branham KE, Othman M, Jakobsdottir J, Tosakulwong N, Pericak-Vance MA, Campochiaro PA, Klein ML, Tan PL, Conley YP, Kanda A, Kopplin L, Li Y, Augustaitis KJ, Karoukis AJ, Scott WK, Agarwal A, Kovach JL, Schwartz SG, Postel EA, Brooks M, Baratz KH, Brown WL, Brucker AJ, Orlin A, Brown G, Ho A, Regillo C, Donoso L, Tian L, Kaderli B, Hadley D, Hagstrom SA, Peachey NS, Klein R, Klein BE, Gotoh N, Yamashiro K, Ferris F Iii, Fagerness JA, Reynolds R, Farrer LA, Kim IK, Miller JW, Corton M, Carracedo A, Sanchez-Salorio M, Pugh EW, Doheny KF, Brion M, Deangelis MM, Weeks DE, Zack DJ, Chew EY, Heckenlively JR, Yoshimura N, Iyengar SK, Francis PJ, Katsanis N, Seddon JM, Haines JL, Gorin MB, Abecasis GR, Swaroop A. Genetic variants near TIMP3 and high-density lipoprotein-associated loci influence susceptibility to age-related macular degeneration. Proc Natl Acad Sci U S A. 2010a; 107(16):7401–7406. [PubMed: 20385819]

Chen Y, Bedell M, Zhang K. Age-related macular degeneration: genetic and environmental factors of disease. Mol Interv. 2010b; 10(5):271–281. [PubMed: 21045241]

Chen Y, Zeng J, Zhao C, Wang K, Trood E, Buehler J, Weed M, Kasuga D, Bernstein PS, Hughes G, Fu V, Chin J, Lee C, Crocker M, Bedell M, Salasar F, Yang Z, Goldbaum M, Ferreyra H, Freeman WR, Kozak I, Zhang K. Assessing susceptibility to age-related macular degeneration with genetic markers and environmental factors. Arch Ophthalmol. 2011; 129(3):344–351. [PubMed: 21402993]

Cho Y, Wang JJ, Chew EY, Ferris FL 3rd, Mitchell P, Chan CC, Tuo J. Toll-like receptor polymorphisms and age-related macular degeneration: replication in three case-control samples. Invest Ophthalmol Vis Sci. 2009; 50(12):5614–5618. [PubMed: 19628747]

Chowers I, Wong R, Dentchev T, Farkas RH, Iacovelli J, Gunatilaka TL, Medeiros NE, Presley JB, Campochiaro PA, Curcio CA, Dunaief JL, Zack DJ. The iron carrier transferrin is upregulated in retinas from patients with age-related macular degeneration. Invest Ophthalmol Vis Sci. 2006; 47(5):2135–2140. [PubMed: 16639025]

Churchill AJ, Carter JG, Lovell HC, Ramsden C, Turner SJ, Yeung A, Escardo J, Atan D. VEGF polymorphisms are associated with neovascular age-related macular degeneration. Human Molecular Genetics. 2006; 15(19):2955–2961. [PubMed: 16940309]

Clark SJ, Perveen R, Hakobyan S, Morgan BP, Sim RB, Bishop PN, Day AJ. Impaired binding of the age-related macular degeneration-associated complement factor H 402H allotype to Bruch';s membrane in human retina. J Biol Chem. 2010; 285(39):30192–30202. [PubMed: 20660596]

DeAngelis MM, Ji F, Kim IK, Adams S, Capone A Jr, Ott J, Miller JW, Dryja TP. Cigarette smoking, CFH, APOE, ELOVL4, and risk of neovascular age-related macular degeneration. Archives of Ophthalmology. 2007; 125(1):49–54. [PubMed: 17210851]

Deangelis MM, Silveira AC, Carr EA, Kim IK. Genetics of age-related macular degeneration: current concepts, future directions. Semin Ophthalmol. 2011; 26(3):77–93. [PubMed: 21609220]

Despriet DD, Bergen AA, Merriam JE, Zernant J, Barile GR, Smith RT, Barbazetto IA, van Soest S, Bakker A, de Jong PT, Allikmets R, Klaver CC. Comprehensive analysis of the candidate genes CCL2, CCR2, and TLR4 in age-related macular degeneration. Invest Ophthalmol Vis Sci. 2008; 49(1):364–371. [PubMed: 18172114]

Ding JD, Johnson LV, Herrmann R, Farsiu S, Smith SG, Groelle M, Mace BE, Sullivan P, Jamison JA, Kelly U, Harrabi O, Bollini SS, Dilley J, Kobayashi D, Kuang B, Li W, Pons J, Lin JC, Bowes Rickman C. Anti-amyloid therapy protects against retinal pigmented epithelium damage and vision loss in a model of age-related macular degeneration. Proc Natl Acad Sci U S A. 2011; 108(28):E279–287. [PubMed: 21690377]

Dinu V, Miller PL, Zhao H. Evidence for association between multiple complement pathway genes and AMD. Genet Epidemiol. 2007; 31(3):224–237. [PubMed: 17266113]

Edwards AO, Chen D, Fridley BL, James KM, Wu Y, Abecasis G, Swaroop A, Othman M, Branham K, Iyengar SK, Sivakumaran TA, Klein R, Klein BE, Tosakulwong N. Toll-like Receptor Polymorphisms and Age-Related Macular Degeneration. Invest Ophthalmol Vis Sci. 2008; 49(4): 1652–1659. [PubMed: 18385087]

Edwards AO, Swaroop A, Seddon JM. Geographic atrophy in age-related macular degeneration and TLR3. N Engl J Med. 2009; 360(21):2254–2255. [PubMed: 19469037]

Edwards DR, Gallins P, Polk M, Ayala-Haedo J, Schwartz SG, Kovach JL, Spencer K, Wang G, Agarwal A, Postel EA, Haines JL, Pericak-Vance M, Scott WK. Inverse association of female hormone replacement therapy with age-related macular degeneration and interactions with ARMS2 polymorphisms. Invest Ophthalmol Vis Sci. 2010; 51(4):1873–1879. [PubMed: 19933179]

Ennis S, Jomary C, Mullins R, Cree A, Chen X, Macleod A, Jones S, Collins A, Stone E, Lotery A. Association between the SERPING1 gene and age-related macular degeneration: a two-stage case-control study. Lancet. 2008; 372(9652):1828–1834. [PubMed: 18842294]

Fafowora, O.; Gorin, M. Genetics of Age-related Maculopathy. In: Traboulsi, E., editor. Genetic Diseases of the Eye. 2. Oxford University Press; New York: 2012a. p. 543-573.

Fafowora, O.; Gorin, MB. Genetics of Age-related Maculopathy. In: Traboulsi, EI., editor. Genetic Diseases of the Eye. 2. Oxford University Press; New York: 2012b. p. 543-573.

Fang AM, Lee AY, Kulkarni M, Osborn MP, Brantley MA Jr. Polymorphisms in the VEGFA and VEGFR-2 genes and neovascular age-related macular degeneration. Mol Vis. 2009; 15:2710–2719. [PubMed: 20019880]

Farwick A, Wellmann J, Stoll M, Pauleikhoff D, Hense HW. Susceptibility genes and progression in age-related maculopathy: a study of single eyes. Invest Ophthalmol Vis Sci. 2010; 51(2):731–736. [PubMed: 19797206]

Fauser S, Smailhodzic D, Caramoy A, van de Ven JP, Kirchhof B, Hoyng CB, Klevering BJ, Liakopoulos S, den Hollander AI. Evaluation of serum lipid concentrations and genetic variants at high-density lipoprotein metabolism loci and TIMP3 in age-related macular degeneration. Invest Ophthalmol Vis Sci. 2011; 52(8):5525–5528. [PubMed: 21613373]

Feigl B, Cao D, Morris CP, Zele AJ. Persons with age-related maculopathy risk genotypes and clinically normal eyes have reduced mesopic vision. Invest Ophthalmol Vis Sci. 2011; 52(2): 1145–1150. [PubMed: 20881291]

Feigl B, Morris CP. The challenge of predicting macular degeneration. Curr Med Res Opin. 2011; 27(9):1745–1748. [PubMed: 21777160]

Fisher SA, Abecasis GR, Yashar BM, Zareparsi S, Swaroop A, Iyengar SK, Klein BE, Klein R, Lee KE, Majewski J, Schultz DW, Klein ML, Seddon JM, Santangelo SL, Weeks DE, Conley YP, Mah TS, Schmidt S, Haines JL, Pericak-Vance MA, Gorin MB, Schulz HL, Pardi F, Lewis CM, Weber BH. Meta-analysis of genome scans of age-related macular degeneration. Hum Mol Genet. 2005; 14(15):2257–2264. [PubMed: 15987700]

Francis PJ, Hamon SC, Ott J, Weleber RG, Klein ML. Polymorphisms in C2, CFB and C3 are associated with progression to advanced age related macular degeneration associated with visual loss. J Med Genet. 2009; 46(5):300–307. [PubMed: 19015224]

Francis PJ, Klein ML. Update on the role of genetics in the onset of age-related macular degeneration. Clin Ophthalmol. 2011; 5:1127–1133. [PubMed: 21887094]

Fritsche LG, Lauer N, Hartmann A, Stippa S, Keilhauer CN, Oppermann M, Pandey MK, Kohl J, Zipfel PF, Weber BH, Skerka C. An imbalance of human complement regulatory proteins CFHR1, CFHR3 and factor H influences risk for age-related macular degeneration (AMD). Hum Mol Genet. 2010; 19(23):4694–4704. [PubMed: 20843825]

Fuse N, Mengkegale M, Miyazawa A, Abe T, Nakazawa T, Wakusawa R, Nishida K. Polymorphisms in ARMS2 (LOC387715) and LOXL1 genes in the Japanese with age-related macular degeneration. Am J Ophthalmol. 2011; 151(3):550–556 e551. [PubMed: 21236409]

Gibson J, Cree A, Collins A, Lotery A, Ennis S. Determination of a gene and environment risk model for age-related macular degeneration. Br J Ophthalmol. 2010; 94(10):1382–1387. [PubMed: 20576771]

Gotoh N, Yamashiro K, Nakanishi H, Saito M, Iida T, Yoshimura N. Haplotype analysis of the ARMS2/HTRA1 region in Japanese patients with typical neovascular age-related macular degeneration or polypoidal choroidal vasculopathy. Jpn J Ophthalmol. 2010; 54(6):609–614. [PubMed: 21191724]

Grassi MA, Folk JC, Scheetz TE, Taylor CM, Sheffield VC, Stone EM. Complement factor H polymorphism p.Tyr402His and cuticular Drusen. Archives of Ophthalmology. 2007; 125(1):93–97. [PubMed: 17210858]

Gu J, Pauer GJ, Yue X, Narendra U, Sturgill GM, Bena J, Gu X, Peachey NS, Salomon RG, Hagstrom SA, Crabb JW. Proteomic and genomic biomarkers for age-related macular degeneration. Adv Exp Med Biol. 2010; 664:411–417. [PubMed: 20238042]

Gu X, Meer SG, Miyagi M, Rayborn ME, Hollyfield JG, Crabb JW, Salomon RG. Carboxyethylpyrrole Protein Adducts and Autoantibodies, Biomarkers for Age-related Macular Degeneration. J Biol Chem. 2003; 278(43):42027–42035. [PubMed: 12923198]

Haas P, Steindl K, Aggermann T, Schmid-Kubista K, Krugluger W, Hageman GS, Binder S. Serum VEGF and CFH in exudative age-related macular degeneration. Curr Eye Res. 2011; 36(2):143–148. [PubMed: 21158586]

Hageman GS, Hancox LS, Taiber AJ, Gehrs KM, Anderson DH, Johnson LV, Radeke MJ, Kavanagh D, Richards A, Atkinson J, Meri S, Bergeron J, Zernant J, Merriam J, Gold B, Allikmets R, Dean M. Extended haplotypes in the complement factor H (CFH) and CFH-related (CFHR) family of genes protect against age-related macular degeneration: characterization, ethnic distribution and evolutionary implications. Ann Med. 2006; 38(8):592–604. [PubMed: 17438673]

Haines JL, Schnetz-Boutaud N, Schmidt S, Scott WK, Agarwal A, Postel EA, Olson L, Kenealy SJ, Hauser M, Gilbert JR, Pericak-Vance MA. Functional candidate genes in age-related macular degeneration: significant association with VEGF, VLDLR, and LRP6. Invest Ophthalmol Vis Sci. 2006; 47(1):329–335. [PubMed: 16384981]

Hayashi H, Yamashiro K, Gotoh N, Nakanishi H, Nakata I, Tsujikawa A, Otani A, Saito M, Iida T, Matsuo K, Tajima K, Yamada R, Yoshimura N. CFH and ARMS2 variations in age-related macular degeneration, polypoidal choroidal vasculopathy, and retinal angiomatous proliferation. Invest Ophthalmol Vis Sci. 2010; 51(11):5914–5919. [PubMed: 20574013]

Ho L, van Leeuwen R, Witteman JC, van Duijn CM, Uitterlinden AG, Hofman A, de Jong PT, Vingerling JR, Klaver CC. Reducing the genetic risk of age-related macular degeneration with dietary antioxidants, zinc, and omega-3 fatty acids: the Rotterdam study. Arch Ophthalmol. 2011; 129(6):758–766. [PubMed: 21670343]

Hu J, Yuan Y, Shen L, Zhang J, Hu N, Guan H. Age-related macular degeneration-susceptibility single nucleotide polymorphisms in a han chinese control population. Ophthalmic Epidemiol. 2011; 18(3):137–142. [PubMed: 21609242]

Hughes AE, Orr N, Esfandiary H, Diaz-Torres M, Goodship T, Chakravarthy U. A common CFH haplotype, with deletion of CFHR1 and CFHR3, is associated with lower risk of age-related macular degeneration. Nature Genetics. 2006; 38(10):1173–1177. [PubMed: 16998489]

Hughes AE, Orr N, Patterson C, Esfandiary H, Hogg R, McConnell V, Silvestri G, Chakravarthy U. Neovascular age-related macular degeneration risk based on CFH, LOC387715/HTRA1, and smoking. PLoS Med. 2007; 4(12):e355. [PubMed: 18162041]

Ikeda T, Obayashi H, Hasegawa G, Nakamura N, Yoshikawa T, Imamura Y, Koizumi K, Kinoshita S. Paraoxonase gene polymorphisms and plasma oxidized low-density lipoprotein level as possible risk factors for exudative age-related macular degeneration. American Journal of Ophthalmology. 2001; 132(2):191–195. [PubMed: 11476678]

Iyengar SK, Song D, Klein BE, Klein R, Schick JH, Humphrey J, Millard C, Liptak R, Russo K, Jun G, Lee KE, Fijal B, Elston RC. Dissection of genomewide-scan data in extended families reveals a major locus and oligogenic susceptibility for age-related macular degeneration. Am J Hum Genet. 2004; 74(1):20–39. [PubMed: 14691731]

Immonen I, Seitsonen S, Tommila P, Kangas-Kontio T, Kakko S, Savolainen ER, Savolainen MJ, Liinamaa MJ. Vascular endothelial growth factor gene variation and the response to photodynamic therapy in age-related macular degeneration. Ophthalmology. 2010; 117(1):103–108. [PubMed: 19896188]

Jakobsdottir J, Conley YP, Weeks DE, Ferrell RE, Gorin MB. C2 and CFB genes in age-related maculopathy and joint action with CFH and LOC387715 genes. PLoS ONE. 2008; 3(5):e2199. [PubMed: 18493315]

Jakobsdottir J, Conley YP, Weeks DE, Mah TS, Ferrell RE, Gorin MB. Susceptibility genes for age-related maculopathy on chromosome 10q26. Am J Hum Genet. 2005; 77(3):389–407. [PubMed: 16080115]

Jakobsdottir J, Gorin MB, Conley YP, Ferrell RE, Weeks DE. Interpretation of genetic association studies: markers with replicated highly significant odds ratios may be poor classifiers. PLoS Genet. 2009; 5(2):e1000337. [PubMed: 19197355]

Jones MM, Manwaring N, Wang JJ, Rochtchina E, Mitchell P, Sue CM. Mitochondrial DNA haplogroups and age-related maculopathy. Arch Ophthalmol. 2007; 125(9):1235–1240. [PubMed: 17846364]

Jun G, Klein BE, Klein R, Fox K, Millard C, Capriotti J, Russo K, Lee KE, Elston RC, Iyengar SK. Genome-wide analyses demonstrate novel Loci that predispose to drusen formation. Invest Ophthalmol Vis Sci. 2005; 46(9):3081–3088. [PubMed: 16123405]

Kanda A, Chen W, Othman M, Branham KE, Brooks M, Khanna R, He S, Lyons R, Abecasis GR, Swaroop A. A variant of mitochondrial protein LOC387715/ARMS2, not HTRA1, is strongly associated with age-related macular degeneration. Proc Natl Acad Sci U S A. 2007; 104(41): 16227–16232. [PubMed: 17884985]

Kaneko H, Dridi S, Tarallo V, Gelfand BD, Fowler BJ, Cho WG, Kleinman ME, Ponicsan SL, Hauswirth WW, Chiodo VA, Kariko K, Yoo JW, Lee DK, Hadziahmetovic M, Song Y, Misra S, Chaudhuri G, Buaas FW, Braun RE, Hinton DR, Zhang Q, Grossniklaus HE, Provis JM, Madigan MC, Milam AH, Justice NL, Albuquerque RJ, Blandford AD, Bogdanovich S, Hirano Y, Witta J, Fuchs E, Littman DR, Ambati BK, Rudin CM, Chong MM, Provost P, Kugel JF, Goodrich JA, Dunaief JL, Baffi JZ, Ambati J. DICER1 deficit induces Alu RNA toxicity in age-related macular degeneration. Nature. 2011; 471(7338):325–330. [PubMed: 21297615]

Katta S, Kaur I, Chakrabarti S. The molecular genetic basis of age-related macular degeneration: an overview. J Genet. 2009; 88(4):425–449. [PubMed: 20090206]

Kenney MC, Atilano SR, Boyer D, Chwa M, Chak G, Chinichian S, Coskun P, Wallace DC, Nesburn AB, Udar NS. Characterization of retinal and blood mitochondrial DNA from age-related macular degeneration patients. Invest Ophthalmol Vis Sci. 2010; 51(8):4289–4297. [PubMed: 20357205]

Kim IK, Ji F, Morrison MA, Adams S, Zhang Q, Lane AM, Capone A, Dryja TP, Ott J, Miller JW, DeAngelis MM. Comprehensive analysis of CRP, CFH Y402H and environmental risk factors on risk of neovascular age-related macular degeneration. Mol Vis. 2008; 14:1487–1495. [PubMed: 18704199]

Klaver CC, Bergen AA. The SERPING1 gene and age-related macular degeneration. Lancet. 2008; 372(9652):1788–1789. [PubMed: 18842295]

Klaver CC, Wolfs RC, Assink JJ, van Duijn CM, Hofman A, de Jong PT. Genetic risk of age-related maculopathy. Population-based familial aggregation study. Archives of Ophthalmology. 1998; 116(12):1646–1651. [PubMed: 9869796]

Klegeris A, McGeer PL. Complement activation by islet amyloid polypeptide (IAPP) and alpha-synuclein 112. Biochem Biophys Res Commun. 2007; 357(4):1096–1099. [PubMed: 17459337]

Klein ML, Ferris FL 3rd, Francis PJ, Lindblad AS, Chew EY, Hamon SC, Ott J. Progression of geographic atrophy and genotype in age-related macular degeneration. Ophthalmology. 2010; 117(8):1554–1559. 1559 e1551. [PubMed: 20381870]

Kleinman ME, Yamada K, Takeda A, Chandrasekaran V, Nozaki M, Baffi JZ, Albuquerque RJ, Yamasaki S, Itaya M, Pan Y, Appukuttan B, Gibbs D, Yang Z, Kariko K, Ambati BK, Wilgus TA, DiPietro LA, Sakurai E, Zhang K, Smith JR, Taylor EW, Ambati J. Sequence- and target-independent angiogenesis suppression by siRNA via TLR3. Nature. 2008; 452(7187):591–597. [PubMed: 18368052]

Kloeckener-Gruissem B, Barthelmes D, Labs S, Schindler C, Kurz-Levin M, Michels S, Fleischhauer J, Berger W, Sutter F, Menghini M. Genetic association with response to intravitreal ranibizumab in patients with neovascular AMD. Invest Ophthalmol Vis Sci. 2011; 52(7):4694–4702. [PubMed: 21282580]

Kokotas H, Grigoriadou M, Petersen MB. Age-related macular degeneration: genetic and clinical findings. Clin Chem Lab Med. 2011; 49(4):601–616. [PubMed: 21175380]

Kondo N, Bessho H, Honda S, Negi A. SOD2 gene polymorphisms in neovascular age-related macular degeneration and polypoidal choroidal vasculopathy. Mol Vis. 2009; 15:1819–1826. [PubMed: 19753309]

Kopplin LJ, Igo RP Jr, Wang Y, Sivakumaran TA, Hagstrom SA, Peachey NS, Francis PJ, Klein ML, SanGiovanni JP, Chew EY, Pauer GJ, Sturgill GM, Joshi T, Tian L, Xi Q, Henning AK, Lee KE, Klein R, Klein BE, Iyengar SK. Genome-wide association identifies SKIV2L and MYRIP as protective factors for age-related macular degeneration. Genes Immun. 2010; 11(8):609–621. [PubMed: 20861866]

Kortvely E, Hauck SM, Duetsch G, Gloeckner CJ, Kremmer E, Alge-Priglinger CS, Deeg CA, Ueffing M. ARMS2 is a constituent of the extracellular matrix providing a link between familial and sporadic age-related macular degenerations. Invest Ophthalmol Vis Sci. 2010; 51(1):79–88. [PubMed: 19696174]

Kralovicova J, Vorechovsky I. SERPING1 rs2511988 and age-related macular degeneration. Lancet. 2009; 373(9662):461–462. [PubMed: 19200915]

Kubicka-Trzaska A, Wilanska J, Romanowska-Dixon B, Sanak M. Circulating antiretinal antibodies predict the outcome of anti-VEGF therapy in patients with exudative age-related macular degeneration. Acta Ophthalmol. 2011

Kubista KE, Tosakulwong N, Wu Y, Ryu E, Roeder JL, Hecker LA, Baratz KH, Brown WL, Edwards AO. Copy number variation in the complement factor H-related genes and age-related macular degeneration. Mol Vis. 2011; 17:2080–2092. [PubMed: 21850184]

Kurji KH, Cui JZ, Lin T, Harriman D, Prasad SS, Kojic L, Matsubara JA. Microarray analysis identifies changes in inflammatory gene expression in response to amyloid-beta stimulation of cultured human retinal pigment epithelial cells. Invest Ophthalmol Vis Sci. 2010; 51(2):1151–1163. [PubMed: 19797223]

Kutty RK, Nagineni CN, Samuel W, Vijayasarathy C, Hooks JJ, Redmond TM. Inflammatory cytokines regulate microRNA-155 expression in human retinal pigment epithelial cells by

activating JAK/STAT pathway. Biochem Biophys Res Commun. 2010; 402(2):390–395. [PubMed: 20950585]

Lauer N, Mihlan M, Hartmann A, Schlotzer-Schrehardt U, Keilhauer C, Scholl HP, Charbel Issa P, Holz F, Weber BH, Skerka C, Zipfel PF. Complement regulation at necrotic cell lesions is impaired by the age-related macular degeneration-associated factor-H His402 risk variant. J Immunol. 2011; 187(8):4374–4383. [PubMed: 21930971]

Lee AY, Kulkarni M, Fang AM, Edelstein S, Osborn MP, Brantley MA. The effect of genetic variants in SERPING1 on the risk of neovascular age-related macular degeneration. Br J Ophthalmol. 2010; 94(7):915–917. [PubMed: 20606025]

Lewin AS. Geographic atrophy in age-related macular degeneration and TLR3. N Engl J Med. 2009; 360(21):2251. [PubMed: 19458376]

Liew G, Mitchell P, Wong TY. Geographic atrophy in age-related macular degeneration and TLR3. N Engl J Med. 2009; 360(21):2252. [PubMed: 19469036]

Lima LH, Schubert C, Ferrara DC, Merriam JE, Imamura Y, Freund KB, Spaide RF, Yannuzzi LA, Allikmets R. Three major loci involved in age-related macular degeneration are also associated with polypoidal choroidal vasculopathy. Ophthalmology. 2010; 117(8):1567–1570. [PubMed: 20378180]

Lin H, Xu H, Liang FQ, Liang H, Gupta P, Havey AN, Boulton ME, Godley BF. Mitochondrial DNA damage and repair in RPE associated with aging and age-related macular degeneration. Invest Ophthalmol Vis Sci. 2011; 52(6):3521–3529. [PubMed: 21273542]

Lin JM, Wan L, Tsai YY, Lin HJ, Tsai Y, Lee CC, Tsai CH, Tseng SH, Tsai FJ. Vascular Endothelial Growth Factor Gene Polymorphisms in Age-related Macular Degeneration. Am J Ophthalmol. 2008

Liu MM, Agron E, Chew E, Meyerle C, Ferris FL 3rd, Chan CC, Tuo J. Copy number variations in candidate genes in neovascular age-related macular degeneration. Invest Ophthalmol Vis Sci. 2011; 52(6):3129–3135. [PubMed: 21273533]

Lu F, Zhao P, Fan Y, Tang S, Hu J, Liu X, Yang X, Chen Y, Li T, Lei C, Yang J, Lin Y, Ma S, Li C, Shi Y, Yang Z. An association study of SERPING1 gene and age-related macular degeneration in a Han Chinese population. Mol Vis. 2010; 16:1–6. [PubMed: 20062564]

Luibl V, Isas JM, Kayed R, Glabe CG, Langen R, Chen J. Drusen deposits associated with aging and age-related macular degeneration contain nonfibrillar amyloid oligomers. J Clin Invest. 2006; 116(2):378–385. [PubMed: 16453022]

Majewski J, Schultz DW, Weleber RG, Schain MB, Edwards AO, Matise TC, Acott TS, Ott J, Klein ML. Age-related macular degeneration--a genome scan in extended families. Am J Hum Genet. 2003; 73(3):540–550. [PubMed: 12900797]

Martinez-Barricarte R, Recalde S, Fernandez-Robredo P, Millan I, Olavarrieta L, Vinuela A, Perez-Perez J, GarciaLayana A, Rodriguez de Cordoba S, AMD tSMGo. Relevance of Complement Factor H,ÄìRelated 1(CFHR1) Genotypes in Age-Related Macular Degeneration. Investigative Ophthalmology & Visual Science. 2012; 53(3):1087–1094. [PubMed: 22247456]

Meyer KJ, Davis LK, Schindler EI, Beck JS, Rudd DS, Grundstad AJ, Scheetz TE, Braun TA, Fingert JH, Alward WL, Kwon YH, Folk JC, Russell SR, Wassink TH, Stone EM, Sheffield VC. Genome-wide analysis of copy number variants in age-related macular degeneration. Hum Genet. 2011; 129(1):91–100. [PubMed: 20981449]

Millen AE, Voland R, Sondel SA, Parekh N, Horst RL, Wallace RB, Hageman GS, Chappell R, Blodi BA, Klein ML, Gehrs KM, Sarto GE, Mares JA. Vitamin D status and early age-related macular degeneration in postmenopausal women. Arch Ophthalmol. 2011; 129(4):481–489. [PubMed: 21482873]

Morrison MA, Silveira AC, Huynh N, Jun G, Smith SE, Zacharaki F, Sato H, Loomis S, Andreoli MT, Adams SM, Radeke MJ, Jelcick AS, Yuan Y, Tsiloulis AN, Chatzoulis DZ, Silvestri G, Kotoula MG, Tsironi EE, Hollis BW, Chen R, Haider NB, Miller JW, Farrer LA, Hageman GS, Kim IK, Schaumberg DA, Deangelis MM. Systems biology-based analysis implicates a novel role for vitamin D metabolism in the pathogenesis of age-related macular degeneration. Hum Genomics. 2011; 5(6):538–568. [PubMed: 22155603]

Nakanishi H, Yamashiro K, Yamada R, Gotoh N, Hayashi H, Nakata I, Saito M, Iida T, Oishi A, Kurimoto Y, Matsuo K, Tajima K, Matsuda F, Yoshimura N. Joint effect of cigarette smoking and CFH and LOC387715/HTRA1 polymorphisms on polypoidal choroidal vasculopathy. Invest Ophthalmol Vis Sci. 2010; 51(12):6183–6187. [PubMed: 20688737]

Nakata I, Yamashiro K, Nakanishi H, Tsujikawa A, Otani A, Yoshimura N. VEGF gene polymorphism and response to intravitreal bevacizumab and triple therapy in age-related macular degeneration. Jpn J Ophthalmol. 2011; 55(5):435–443. [PubMed: 21744122]

Narendra U, Pauer GJ, Hagstrom SA. Genetic analysis of complement factor H related 5, CFHR5, in patients with age-related macular degeneration. Mol Vis. 2009; 15:731–736. [PubMed: 19365580]

Neale BM, Fagerness J, Reynolds R, Sobrin L, Parker M, Raychaudhuri S, Tan PL, Oh EC, Merriam JE, Souied E, Bernstein PS, Li B, Frederick JM, Zhang K, Brantley MA Jr, Lee AY, Zack DJ, Campochiaro B, Campochiaro P, Ripke S, Smith RT, Barile GR, Katsanis N, Allikmets R, Daly MJ, Seddon JM. Genome-wide association study of advanced age-related macular degeneration identifies a role of the hepatic lipase gene(LIPC). Proc Natl Acad Sci U S A. 2010; 107(16): 7395–7400. [PubMed: 20385826]

Okamoto H, Umeda S, Nozawa T, Suzuki MT, Yoshikawa Y, Matsuura ET, Iwata T. Comparative proteomic analyses of macular and peripheral retina of cynomolgus monkeys (Macaca fascicularis). Exp Anim. 2010; 59(2):171–182. [PubMed: 20484850]

Ormsby RJ, Ranganathan S, Tong JC, Griggs KM, Dimasi DP, Hewitt AW, Burdon KP, Craig JE, Hoh J, Gordon DL. Functional and Structural Implications of the Complement Factor H Y402H Polymorphism Associated with Age-Related Macular Degeneration. Invest Ophthalmol Vis Sci. 2008; 49(5):1763–1770. [PubMed: 18263814]

Parekh N, Chappell RJ, Millen AE, Albert DM, Mares JA. Association between vitamin D and age-related macular degeneration in the Third National Health and Nutrition Examination Survey, 1988 through 1994. Arch Ophthalmol. 2007; 125(5):661–669. [PubMed: 17502506]

Park KH, Ryu E, Tosakulwong N, Wu Y, Edwards AO. Common variation in the SERPING1 gene is not associated with age-related macular degeneration in two independent groups of subjects. Mol Vis. 2009; 15:200–207. [PubMed: 19169411]

Parmeggiani F, Costagliola C, Incorvaia C, Sebastiani A, Gemmati D. Pharmacogenetic aspects in therapeutic management of subfoveal choroidal neovascularisation: role of factor XIII-A 185 T-allele. Curr Drug Targets. 2011; 12(2):138–148. [PubMed: 20887247]

Pauer GJ, Sturgill GM, Peachey NS, Hagstrom SA. Protective effect of paraoxonase 1 gene variant Gln192Arg in age-related macular degeneration. Am J Ophthalmol. 2010; 149(3):513–522. [PubMed: 20042177]

Qu Y, Dai H, Zhou F, Zhang X, Xu X, Bi H, Pan X, Wang H, Jiang H, Yin N, Dang G. Vascular endothelial growth factor gene polymorphisms and risk of neovascular age-related macular degeneration in a Chinese cohort. Ophthalmic Res. 2011; 45(3):142–148. [PubMed: 20847577]

Raychaudhuri S, Ripke S, Li M, Neale BM, Fagerness J, Reynolds R, Sobrin L, Swaroop A, Abecasis G, Seddon JM, Daly MJ. Associations of CFHR1-CFHR3 deletion and a CFH SNP to age-related macular degeneration are not independent. Nat Genet. 2010; 42(7):553–555. [PubMed: 20581873]

Reynolds R, Hartnett ME, Atkinson JP, Giclas PC, Rosner B, Seddon JM. Plasma complement components and activation fragments: associations with age-related macular degeneration genotypes and phenotypes. Invest Ophthalmol Vis Sci. 2009; 50(12):5818–5827. [PubMed: 19661236]

Reynolds R, Rosner B, Seddon JM. Serum lipid biomarkers and hepatic lipase gene associations with age-related macular degeneration. Ophthalmology. 2010; 117(10):1989–1995. [PubMed: 20888482]

Richardson AJ, Islam FM, Guymer RH, Cain M, Baird PN. A tag-single nucleotide polymorphisms approach to the vascular endothelial growth factor-A gene in age-related macular degeneration. Mol Vis. 2007; 13:2148–2152. [PubMed: 18079689]

Rivera A, Fisher SA, Fritsche LG, Keilhauer CN, Lichtner P, Meitinger T, Weber BH. Hypothetical LOC387715 is a second major susceptibility gene for age-related macular degeneration,

contributing independently of complement factor H to disease risk. Human Molecular Genetics. 2005; 14(21):3227–3236. [PubMed: 16174643]

Robman L, Baird PN, Dimitrov PN, Richardson AJ, Guymer RH. C-reactive protein levels and complement factor H polymorphism interaction in age-related macular degeneration and its progression. Ophthalmology. 2010; 117(10):1982–1988. [PubMed: 20605213]

Roca-Santiago HM, Lago-Bouza JR, Millan-Calenti JC, Gomez-Ulla-Irazazabal F. Alzheimer's disease and age-related macular degeneration. Arch Soc Esp Oftalmol. 2006; 81(2):73–78. [PubMed: 16511713]

SanGiovanni JP, Arking DE, Iyengar SK, Elashoff M, Clemons TE, Reed GF, Henning AK, Sivakumaran TA, Xu X, DeWan A, Agron E, Rochtchina E, Sue CM, Wang JJ, Mitchell P, Hoh J, Francis PJ, Klein ML, Chew EY, Chakravarti A. Mitochondrial DNA variants of respiratory complex I that uniquely characterize haplogroup T2 are associated with increased risk of age-related macular degeneration. PLoS ONE. 2009; 4(5):e5508. [PubMed: 19434233]

Santangelo SL, Yen CH, Haddad S, Fagerness J, Huang C, Seddon JM. A discordant sib-pair linkage analysis of age-related macular degeneration. Ophthalmic Genet. 2005; 26(2):61–67. [PubMed: 16020308]

Schaumberg DA, Chasman D, Morrison MA, Adams SM, Guo Q, Hunter DJ, Hankinson SE, DeAngelis MM. Prospective study of common variants in the retinoic acid receptor-related orphan receptor alpha gene and risk of neovascular age-related macular degeneration. Arch Ophthalmol. 2010; 128(11):1462–1471. [PubMed: 21060049]

Schaumberg DA, Hankinson SE, Guo Q, Rimm E, Hunter DJ. A prospective study of 2 major age-related macular degeneration susceptibility alleles and interactions with modifiable risk factors. Archives of Ophthalmology. 2007; 125(1):55–62. see comment. [PubMed: 17210852]

Schick JH, Iyengar SK, Klein BE, Klein R, Reading K, Liptak R, Millard C, Lee KE, Tomany SC, Moore EL, Fijal BA, Elston RC. A whole-genome screen of a quantitative trait of age-related maculopathy in sibships from the Beaver Dam Eye Study. Am J Hum Genet. 2003; 72(6):1412–1424. [PubMed: 12717633]

Schmid-Kubista KE, Tosakulwong N, Wu Y, Ryu E, Hecker LA, Baratz KH, Brown WL, Edwards AO. Contribution of copy number variation in the regulation of complement activation locus to development of age-related macular degeneration. Invest Ophthalmol Vis Sci. 2009; 50(11): 5070–5079. [PubMed: 19553609]

Schmidt S, Hauser MA, Scott WK, Postel EA, Agarwal A, Gallins P, Wong F, Chen YS, Spencer K, Schnetz-Boutaud N, Haines JL, Pericak-Vance MA. Cigarette smoking strongly modifies the association of LOC387715 and age-related macular degeneration. Am J Hum Genet. 2006; 78(5): 852–864. [PubMed: 16642439]

Scholl HP, Charbel Issa P, Walier M, Janzer S, Pollok-Kopp B, Borncke F, Fritsche LG, Chong NV, Fimmers R, Wienker T, Holz FG, Weber BH, Oppermann M. Systemic complement activation in age-related macular degeneration. PLoS ONE. 2008; 3(7):e2593. [PubMed: 18596911]

Seddon JM, Gensler G, Rosner B. C-reactive protein and CFH, ARMS2/HTRA1 gene variants are independently associated with risk of macular degeneration. Ophthalmology. 2010; 117(8):1560–1566. [PubMed: 20346514]

Seddon JM, Reynolds R, Maller J, Fagerness JA, Daly MJ, Rosner B. Prediction Model for Prevalence and Incidence of Advanced Age-Related Macular Degeneration Based on Genetic, Demographic, and Environmental Variables. Invest Ophthalmol Vis Sci. 2008

Seddon JM, Reynolds R, Maller J, Fagerness JA, Daly MJ, Rosner B. Prediction model for prevalence and incidence of advanced age-related macular degeneration based on genetic, demographic, and environmental variables. Invest Ophthalmol Vis Sci. 2009a; 50(5):2044–2053. [PubMed: 19117936]

Seddon JM, Reynolds R, Rosner B. Peripheral retinal drusen and reticular pigment: association with CFHY402H and CFHrs1410996 genotypes in family and twin studies. Invest Ophthalmol Vis Sci. 2009b; 50(2):586–591. [PubMed: 18936151]

Seddon JM, Reynolds R, Yu Y, Daly MJ, Rosner B. Risk models for progression to advanced age-related macular degeneration using demographic, environmental, genetic, and ocular factors. Ophthalmology. 2011; 118(11):2203–2211. [PubMed: 21959373]

Seddon JM, Santangelo SL, Book K, Chong S, Cote J. A genomewide scan for age-related macular degeneration provides evidence for linkage to several chromosomal regions. Am J Hum Genet. 2003; 73(4):780–790. [PubMed: 12945014]

Shastry BS. Genetic diversity and medicinal drug response in eye care. Graefes Arch Clin Exp Ophthalmol. 2010; 248(8):1057–1061. [PubMed: 20204657]

Silveira AC, Morrison MA, Ji F, Xu H, Reinecke JB, Adams SM, Arneberg TM, Janssian M, Lee JE, Yuan Y, Schaumberg DA, Kotoula MG, Tsironi EE, Tsiloulis AN, Chatzoulis DZ, Miller JW, Kim IK, Hageman GS, Farrer LA, Haider NB, DeAngelis MM. Convergence of linkage, gene expression and association data demonstrates the influence of the RAR-related orphan receptor alpha (RORA) gene on neovascular AMD: a systems biology based approach. Vision Res. 2010; 50(7):698–715. [PubMed: 19786043]

Smith RT, Merriam JE, Sohrab MA, Pumariega NM, Barile G, Blonska AM, Haans R, Madigan D, Allikmets R. Complement factor H 402H variant and reticular macular disease. Arch Ophthalmol. 2011; 129(8):1061–1066. [PubMed: 21825189]

Sng CC, Cackett PD, Yeo IY, Thalamuthu A, Venkatraman A, Venkataraman D, Koh AH, Tai ES, Wong TY, Aung T, Vithana EN. Toll-like receptor 3 polymorphism rs3775291 is not associated with choroidal neovascularization or polypoidal choroidal vasculopathy in Chinese subjects. Ophthalmic Res. 2011; 45(4):191–196. [PubMed: 21079408]

Sobrin L, Reynolds R, Yu Y, Fagerness J, Leveziel N, Bernstein PS, Souied EH, Daly MJ, Seddon JM. ARMS2/HTRA1 locus can confer differential susceptibility to the advanced subtypes of age-related macular degeneration. Am J Ophthalmol. 2011; 151(2):345–352 e343. [PubMed: 21122828]

Spencer KL, Hauser MA, Olson LM, Schmidt S, Scott WK, Gallins P, Agarwal A, Postel EA, Pericak-Vance MA, Haines JL. Deletion of CFHR3 and CFHR1 genes in age-related macular degeneration. Hum Mol Genet. 2008; 17(7):971–977. [PubMed: 18084039]

Spencer KL, Olson LM, Schnetz-Boutaud N, Gallins P, Agarwal A, Iannaccone A, Kritchevsky SB, Garcia M, Nalls MA, Newman AB, Scott WK, Pericak-Vance MA, Haines JL. Using genetic variation and environmental risk factor data to identify individuals at high risk for age-related macular degeneration. PLoS ONE. 2011; 6(3):e17784. [PubMed: 21455292]

Stanton CM, Chalmers KJ, Wright AF. The chromosome 10q26 susceptibility locus in age-related macular degeneration. Adv Exp Med Biol. 2012; 723:365–370. [PubMed: 22183354]

Suuronen T, Nuutinen T, Ryhanen T, Kaarniranta K, Salminen A. Epigenetic regulation of clusterin/apolipoprotein J expression in retinal pigment epithelial cells. Biochem Biophys Res Commun. 2007; 357(2):397–401. [PubMed: 17420006]

Synowiec E, Szaflik J, Chmielewska M, Wozniak K, Sklodowska A, Waszczyk M, Dorecka M, Blasiak J, Szaflik JP. An association between polymorphism of the heme oxygenase-1 and -2 genes and age-related macular degeneration. Mol Biol Rep. 2011

Tanaka K, Nakayama T, Mori R, Sato N, Kawamura A, Mizutani Y, Yuzawa M. Associations of complement factor H (CFH) and age-related maculopathy susceptibility 2 (ARMS2) genotypes with subtypes of polypoidal choroidal vasculopathy. Invest Ophthalmol Vis Sci. 2011; 52(10): 7441–7444. [PubMed: 21896867]

Teper SJ, Nowinska A, Pilat J, Palucha A, Wylegala E. Involvement of genetic factors in the response to a variable-dosing ranibizumab treatment regimen for age-related macular degeneration. Mol Vis. 2010; 16:2598–2604. [PubMed: 21151600]

Tong Y, Liao J, Zhang Y, Zhou J, Zhang H, Mao M. LOC387715/HTRA1 gene polymorphisms and susceptibility to age-related macular degeneration: A HuGE review and meta-analysis. Mol Vis. 2010; 16:1958–1981. [PubMed: 21031019]

Tsuchihashi T, Mori K, Horie-Inoue K, Gehlbach PL, Kabasawa S, Takita H, Ueyama K, Okazaki Y, Inoue S, Awata T, Katayama S, Yoneya S. Complement factor H and high-temperature requirement A-1 genotypes and treatment response of age-related macular degeneration. Ophthalmology. 2011; 118(1):93–100. [PubMed: 20678803]

Udar N, Atilano SR, Memarzadeh M, Boyer DS, Chwa M, Lu S, Maguen B, Langberg J, Coskun P, Wallace DC, Nesburn AB, Khatibi N, Hertzog D, Le K, Hwang D, Kenney MC. Mitochondrial DNA haplogroups associated with age-related macular degeneration. Invest Ophthalmol Vis Sci. 2009; 50(6):2966–2974. [PubMed: 19151382]

Vierkotten S, Muether PS, Fauser S. Overexpression of HTRA1 leads to ultrastructural changes in the elastic layer of Bruch's membrane via cleavage of extracellular matrix components. PLoS ONE. 2011; 6(8):e22959. [PubMed: 21829675]

Vingerling JR, Dielemans I, Bots ML, Hofman A, Grobbee DE, de Jong PT. Age-related macular degeneration is associated with atherosclerosis. The Rotterdam Study. American Journal of Epidemiology. 1995; 142(4):404–409. [PubMed: 7625405]

Wang AL, Lukas TJ, Yuan M, Neufeld AH. Increased mitochondrial DNA damage and down-regulation of DNA repair enzymes in aged rodent retinal pigment epithelium and choroid. Mol Vis. 2008a; 14:644–651. [PubMed: 18392142]

Wang G, Scott WK, Whitehead P, Court BL, Kovach JL, Schwartz SG, Agarwal A, Dubovy S, Haines JL, Pericak-Vance MA. A novel ARMS2 splice variant is identified in human retina. Exp Eye Res. 2012; 94(1):187–191. [PubMed: 22138417]

Wang G, Spencer KL, Court BL, Olson LM, Scott WK, Haines JL, Pericak-Vance MA. Localization of age-related macular degeneration-associated ARMS2 in cytosol, not mitochondria. Invest Ophthalmol Vis Sci. 2009a; 50(7):3084–3090. [PubMed: 19255159]

Wang G, Spencer KL, Scott WK, Whitehead P, Court BL, Ayala-Haedo J, Mayo P, Schwartz SG, Kovach JL, Gallins P, Polk M, Agarwal A, Postel EA, Haines JL, Pericak-Vance MA. Analysis of the indel at the ARMS2 3'UTR in age-related macular degeneration. Hum Genet. 2010; 127(5):595–602. [PubMed: 20182747]

Wang J, Ohno-Matsui K, Yoshida T, Kojima A, Shimada N, Nakahama K, Safranova O, Iwata N, Saido TC, Mochizuki M, Morita I. Altered function of factor I caused by amyloid beta: implication for pathogenesis of age-related macular degeneration from Drusen. J Immunol. 2008b; 181(1):712–720. [PubMed: 18566438]

Wang J, Ohno-Matsui K, Yoshida T, Shimada N, Ichinose S, Sato T, Mochizuki M, Morita I. Amyloid-beta up-regulates complement factor B in retinal pigment epithelial cells through cytokines released from recruited macrophages/microglia: Another mechanism of complement activation in age-related macular degeneration. J Cell Physiol. 2009b; 220(1):119–128. [PubMed: 19277984]

Weeks DE, Conley YP, Mah TS, Paul TO, Morse L, Ngo-Chang J, Dailey JP, Ferrell RE, Gorin MB. A full genome scan for age-related maculopathy. Hum Mol Genet. 2000; 9(9):1329–1349. [PubMed: 10814715]

Weeks DE, Conley YP, Tsai HJ, Mah TS, Rosenfeld PJ, Paul TO, Eller AW, Morse LS, Dailey JP, Ferrell RE, Gorin MB. Age-related maculopathy: an expanded genome-wide scan with evidence of susceptibility loci within the 1q31 and 17q25 regions. Am J Ophthalmol. 2001; 132(5):682–692. [PubMed: 11704029]

Weeks DE, Conley YP, Tsai HJ, Mah TS, Schmidt S, Postel EA, Agarwal A, Haines JL, Pericak-Vance MA, Rosenfeld PJ, Paul TO, Eller AW, Morse LS, Dailey JP, Ferrell RE, Gorin MB. Age-related maculopathy: a genomewide scan with continued evidence of susceptibility loci within the 1q31, 10q26, and 17q25 regions. Am J Hum Genet. 2004; 75(2):174–189. [PubMed: 15168325]

Wegscheider BJ, Weger M, Renner W, Steinbrugger I, Marz W, Mossbock G, Temmel W, El-Shabrawi Y, Schmut O, Jahrbacher R, Haas A. Association of complement factor H Y402H gene polymorphism with different subtypes of exudative age-related macular degeneration. Ophthalmology. 2007; 114(4):738–742. [PubMed: 17398321]

Weismann D, Hartvigsen K, Lauer N, Bennett KL, Scholl HP, Charbel Issa P, Cano M, Brandstatter H, Tsimikas S, Skerka C, Superti-Furga G, Handa JT, Zipfel PF, Witztum JL, Binder CJ. Complement factor H binds malondialdehyde epitopes and protects from oxidative stress. Nature. 2011; 478(7367):76–81. [PubMed: 21979047]

Wong RW, Richa DC, Hahn P, Green WR, Dunaief JL. Iron toxicity as a potential factor in AMD. Retina. 2007; 27(8):997–1003. [PubMed: 18040235]

Wysokinski D, Synowiec E, Chmielewska M, Wozniak K, Zaras M, Sklodowska A, Blasiak J, Szaflik J, Szaflik JP. Lack of association between the c.544G>A polymorphism of the heme oxygenase-2 gene and age-related macular degeneration. Med Sci Monit. 2011a; 17(8):CR449–455. [PubMed: 21804464]

Wysokinski D, Szaflik J, Sklodowska A, Kolodziejska U, Dorecka M, Romaniuk D, Wozniak K, Blasiak J, Szaflik JP. The A Allele of the -576G>A polymorphism of the transferrin gene is associated with the increased risk of age-related macular degeneration in smokers. Tohoku J Exp Med. 2011b; 223(4):253–261. [PubMed: 21422745]

Yamashiro K, Mori K, Nakata I, Tsuchihashi T, Horie-Inoue K, Nakanishi H, Tsujikawa A, Saito M, Iida T, Yamada R, Matsuda F, Inoue S, Awata T, Yoneya S, Yoshimura N. Association of elastin gene polymorphism to age-related macular degeneration and polypoidal choroidal vasculopathy. Invest Ophthalmol Vis Sci. 2011; 52(12):8780–8784. [PubMed: 22003121]

Yang Z, Stratton C, Francis PJ, Kleinman ME, Tan PL, Gibbs D, Tong Z, Chen H, Constantine R, Yang X, Chen Y, Zeng J, Davey L, Ma X, Hau VS, Wang C, Harmon J, Buehler J, Pearson E, Patel S, Kaminoh Y, Watkins S, Luo L, Zabriskie NA, Bernstein PS, Cho W, Schwager A, Hinton DR, Klein ML, Hamon SC, Simmons E, Yu B, Campochiaro B, Sunness JS, Campochiaro P, Jorde L, Parmigiani G, Zack DJ, Katsanis N, Ambati J, Zhang K. Toll-like receptor 3 and geographic atrophy in age-related macular degeneration. N Engl J Med. 2008; 359(14):1456–1463. [PubMed: 18753640]

Yu Y, Bhangale TR, Fagerness J, Ripke S, Thorleifsson G, Tan PL, Souied EH, Richardson AJ, Merriam JE, Buitendijk GH, Reynolds R, Raychaudhuri S, Chin KA, Sobrin L, Evangelou E, Lee PH, Lee AY, Leveziel N, Zack DJ, Campochiaro B, Campochiaro P, Smith RT, Barile GR, Guymer RH, Hogg R, Chakravarthy U, Robman LD, Gustafsson O, Sigurdsson H, Ortmann W, Behrens TW, Stefansson K, Uitterlinden AG, van Duijn CM, Vingerling JR, Klaver CC, Allikmets R, Brantley MA Jr, Baird PN, Katsanis N, Thorsteinsdottir U, Ioannidis JP, Daly MJ, Graham RR, Seddon JM. Common variants near FRK/COL10A1 and VEGFA are associated with advanced age-related macular degeneration. Hum Mol Genet. 2011; 20(18):3699–3709. [PubMed: 21665990]

Yu Y, Reynolds R, Rosner B, Daly MJ, Seddon JM. Prospective Assessment of Genetic Effects on Progression to Different Stages of Age-Related Macular Degeneration Using Multistate Markov Models. Investigative Ophthalmology & Visual Science. 2012; 53(3):1548–1556. [PubMed: 22247473]

Zareparsi S, Buraczynska M, Branham KE, Shah S, Eng D, Li M, Pawar H, Yashar BM, Moroi SE, Lichter PR, Petty HR, Richards JE, Abecasis GR, Elner VM, Swaroop A. Toll-like receptor 4 variant D299G is associated with susceptibility to age-related macular degeneration. Hum Mol Genet. 2005; 14(11):1449–1455. [PubMed: 15829498]

Zeng J, Chen Y, Tong Z, Zhou X, Zhao C, Wang K, Hughes G, Kasuga D, Bedell M, Lee C, Ferreyra H, Kozak I, Haw W, Guan J, Shaw R, Stevenson W, Weishaar PD, Nelson MH, Tang L, Zhang K. Lack of association of CFD polymorphisms with advanced age-related macular degeneration. Mol Vis. 2010; 16:2273–2278. [PubMed: 21139680]

Zhang X, Wen F, Zuo C, Li M, Chen H, Wu K. Association of genetic variation on chromosome 9p21 with polypoidal choroidal vasculopathy and neovascular age-related macular degeneration. Invest Ophthalmol Vis Sci. 2011; 52(11):8063–8067. [PubMed: 21896860]

Zhou P, Fan L, Yu KD, Zhao MW, Li XX. Toll-like receptor 3 C1234T may protect against geographic atrophy through decreased dsRNA binding capacity. Faseb J. 2011; 25(10):3489–3495. [PubMed: 21712495]

Table 1

Chromosomal Loci with linkage to AMD based on family studies and corresponding candidate genes as determined by case-control association studies

Linkage Study	**Chromosomal Loci (Chromosomes 1 – 8)**													
WEEKS (Weeks et al., 2000)											5q32			
WEEKS (Weeks et al., 2001)	1q31													
WEEKS (Weeks et al., 2004)														
SCHICK (Schick et al., 2003)	1q31		2q14.3											
MAJEWSKI (Majewski et al., 2003)					3					5q12 - 13			6q14-21	
BARRAL (Barral et al., 2006)	1q31				3p13			4q32						
ABECASIS (Abecasis et al., 2004)	1q				3p								6q25.2	
IYENGAR (Iyengar et al., 2004)	1q	2p							5p					
SEDDON (Seddon et al., 2003)	1q31	2p21					4p16				5q34			
SANTANGELO* (Santangelo et al., 2005)	1q	2p24		2q37		3q						6p		8p23
JUN# (Jun et al., 2005)	1q25-q31			2q31-32									6q25.3	
Possible genes within the linkage locus(loci)	CFH 1q32			CYP27A1 2q37 MREG 2q35	MYRIP 3p22 ROBO1 3p12	COL8A1 3q12.3		CFI 4q25	C7 5p13			C2/BF 6p21 VEGFA 6p12	FRK COL10A 6q21	LPL 8p21.3
Linkage Study	Chromosomal Loci (Chromosomes 9 – 22)													
WEEKS (Weeks et al., 2000)			10q26											
WEEKS (Weeks et al., 2001)	9p13		10q26							17q25				
WEEKS (Weeks et al., 2004)			10q26							17q25				

Linkage Study	Chromosomal Loci (Chromosomes 1 – 8)													
SCHICK (Schick et al., 2003)			10q26							17q25				
MAJEWSKI (Majewski et al., 2003)					12q23- 24		15q11-14 15q25-26	16						
BARRAL (Barral et al., 2006)		9q33	10q26											
ABECASIS (Abecasis et al., 2004)		9q	10q											
IYENGAR (Iyengar et al., 2004)		9q												22q
SEDDON (Seddon et al., 2003)	9p24	9q31	10q26	12q13	12q23		15q21	16p1 2			18p11		20q13	
SANTANGELO* (Santangelo et al., 2005)			10q	12q13					16q					22
JUN# (Jun et al., 2005)												19p13	20q13	
Possible genes within the linkage locus(loci)		ABCA1 9q31 CoL15A1 TGFBR1 9q22.33	ARMS2 HTRA1 10q26		SCARB1 12q24.3 1		LIPC 15q21.3 IGF1R 15q26.3		CETP 16q21			C3 19p13		TIMP-3 22q12.3

Table 2

Genes associated with the Alternative Complement Pathway

Gene	Name	Ensemble cytogenetic band	Case-Control Assoc with AMD	Within reported region of AMD linkage	Associated with Other MD, other potential roles
Alternative Complement Pathway Components					
C1QA	Complement component 1, q subcomponent, A chain	1p36.12	-	-	**C1q** associates with C1r and C1s to form C1. Deficiency of **C1q** has been associated with lupus erythematosus and glomerulonephritis.
C1QB	Complement component 1, q subcomponent, B chain	1p36.12	-	-	**C1q** associates with the proenzymes C1r and C1s to yield C1
C1QC	Complement component 1, q subcomponent, C chain	1p36.12	-	-	**C1q** associates with the proenzymes C1r and C1s to yield C1
C1QBP	Complement component 1, q subcomponent binding protein	17p13.2	-	-	**C1q** associates with the proenzymes C1r and C1s to yield C1. Also is p32 subunit of pre-mRNA splicing factor SF2, as well as a hyaluronic acid-binding protein
C1R	Complement component 1, r subcomponent	12p13.31	-	-	a serine protease that combines with C1q and C1s to form C1,
C1S	Complement component 1 subcomponent s	12p13.31	-	-	a serine protease, which is a major constituent of the human complement subcomponent C1.
C2	Complement component 2' C3/C5 convertase	6p21.33	+	+	Also a major histocompatibility complex class-III protein
C3	Complement component 3	19p13.3	+	+	C3 plays a central role in the activation of the complement system.after cleavage by C3 convertase
C5	Complement component 5	9q33.2	-	+	C5 is activated by C5 convertase to initiate the assembly of the late complement components, C5-C9, into the membrane attack complex.
C6	Complement component 6	5p13.1	-	-	Constituent of the membrane attack complex (MAC)
C7	Complement component 7	5p13.1	+	+	The protein participates in the formation of Membrane Attack Complex (MAC).
C8A	Complement component 8 subunit alpha	1p32.2	-	-	Alpha subunit of C8. C8 is part of membrane attack complex (MAC)
C8B	Complement component 8 subunit beta	1p32.2	-	-	Beta subunit of C8. C8 is part of membrane attack complex (MAC)
C8G	Complement component 8 subunit gamma	9q34.3	-	+	Gamma subunit of C8. C8 is part of membrane attack complex (MAC)
C9	Complement component 9	5p13.1	-	+	C9 is the pore-forming subunit of the membrane attack complex (MAC)
Complement Regulatory Factors					
CFH	Complement factor H	1q31.3	+	+	Hemolytic-uremic syndrome

Gene	Name	Ensemble cytogenetic band	Case-Control Assoc with AMD	Within reported region of AMD linkage	Associated with Other MD, other potential roles
CFHR1	Complement factor H-related 1	1q31.3	+	+	Might be involved in complement regulation. Binds lipoproteins and may play a role in lipid metabolism
CFHR2	Complement factor H-related 2	1q31.3	+	+	Might be involved in complement regulation. Binds lipoproteins and may play a role in lipid metabolism
CFHR3	Complement factor H-related	1q31.3	+	+	Active in complement regulation
CFHR4	Complement factor H-related 4	1q31.3	+	+	Binds lipoproteins and may play a role in lipid metabolism
CFHR5	Complement factor H-related 5	1q31.3	+	+	Active in complement regulation
CFB	Complement factor B	6p21.33	+	+	Factor B is cleaved by factor D into 2 fragments: Ba and Bb, a serine protease that associates with C3b
CFP	Complement factor properdin	Xp11.23	-	-	Plasma glycoprotein that positively regulates the alternative complement pathway
CFI	Complement factor I	4q25	+	(+)	Cleaves the alpha-chains of C4b and C3b in the presence of C4-binding protein and factor H respectively. Associated with atypical hemolytic uremic syndrome glomerulonephritis.
SERPING1	Serpin peptidase inhibitor, clade G (C1 inhibitor), member 1	11q12.1	+/-	+	The protein inhibits activated C1r and C1s and regulates complement activation. Assoc. with hereditary angioneurotic edema

Table 3

Genes associated with the Extracellular Matrix and Basement Membrane structure and maintenance

Gene	Name	Ensemble cytogenetic band	Case-Control Assoc with AMD	Within reported region of AMD linkage	Assoc with Juv. MD	Reference
ELN	Elastin	7q11.23	+			(Kondo et al., 2008; Lima et al., 2011; Vierkotten et al., 2011; Yamashiro et al., 2011)
COL10A1	Collagen, type X, alpha 1	6q22.1	+	+		(Yu et al., 2011a)
HMCN1	Hemicentin-1, Fibulin-6	1q25.3	+	+		(Schultz et al., 2003)
ARMS2	Age-related maculopathy susceptibility 2	10q26.13	+	+		(Kortvely et al., 2010)
TIMP3	Tissue inhibitor of metalloproteinase-3	22q12.3	+	+	Sorsby Fundus Dystrophy	(Chen et al., 2010a; Fauser et al., 2011; Lin et al., 2006)
SELP	Selectin-P	1q24.2	(+)	-		(Mullins et al., 2011)
ROBO1	Roundabout, axon guidance receptor, homolog 1	3p12.2	+	+		(Schaumberg et al., 2010; Silveira et al., 2010)
EFEMP1	EGF-containing fibulin-like extracellular matrix protein, Fibulin-3	2p16.1	-	-	Malattia Leventinese, Doyne Honeycomb Retinal Dystrophy	(Fu et al., 2007; Narendran et al., 2005)
FBLN5	Fibulin-5	14q32.12	+	-		(Auer-Grumbach et al., 2011; Stone et al., 2004)
LOXL1	Lysyl oxidase-like 1	15q24.1	+/-	-		(Fuse et al., 2011; Lepre et al., 2011; Sakurada et al., 2011)
C1QTNF5	CRTP5, complement C1q tumor necrosis factor-related protein 5	11q23.3	-	-	Late-onset retinal degeneration (LORD, L-ORMD)	(Ayyagari et al., 2005; Shu et al., 2006a; Shu et al., 2006b)
COL8A1	Collagen, type VIII, alpha 1	3q12.1	(+)	+		(Yu et al., 2011a)
COL15A1*	Collagen, type XV, alpha 1	9q22.33	+	+		AMD consortium

Table 4

Genes associated with lipid and/or retinoid metabolic pathways

Gene	Name	Ensemble cytogenetic band	"Known" Function	Reference
LIPC	Hepatic lipase, Lipase member C	15q21.3	Hepatic triglyceride lipase functions as a triglyceride hydrolase and as a ligand/ bridging factor for receptor-mediated lipoprotein transport	(Chen et al., 2010a; Neale et al., 2010; Peter et al., 2011; Yu et al., 2011a; Yu et al., 2011b)
CETP	Cholesteryl ester transfer protein	16q13	Transfers cholesteryl esters between lipoproteins	(Chen et al., 2010a; Yu et al., 2011a)
ApoE	Apolipoprotein E	19q13.32	The main apoprotein of the chylomicron, binds to a specific receptor on liver cells and peripheral cells. ApoE mediates the binding, internalization, and catabolism of lipoprotein particles.	(Chen et al., 2010a; Neale et al., 2010; Zerbib et al., 2009)
LRP5	Low-density lipoprotein receptor-related protein 5	11q13.2	The gene encodes a transmembrane low-density lipoprotein receptor that binds and internalizes ligands in the process of receptor-mediated endocytosis.	(Kloeckener-Gruissem et al., 2011)
LRP6	Low-density lipoprotein receptor-related protein 6	12p13.2	The gene encodes a transmembrane low-density lipoprotein receptor that binds and internalizes ligands in the process of receptor-mediated endocytosis.	(Haines et al., 2006)
VDLR	Very low density lipoprotein receptor	9p24.2	Lipoprotein receptor that is a member of the LDLR family and binds VLDL-triglyceride and transports it into cells by endocytosis and is key player in the reelin signaling pathway.	(Haines et al., 2006)
FADS1-3	Fatty acid desaturase 1,2, and 3	11q12.2	Members of the fatty acid desaturase (FADS) gene family. These enzymes regulate unsaturation of fatty acids through the introduction of double bonds between defined carbons of the fatty acyl chain. They are in a gene cluster on 11q12.2	(Fauser et al., 2011)
ABCA1	ATP-binding cassette transporter-1	9q31.1	Cholesterol efflux transporter for lipid removal from cells	(Fauser et al., 2011)
RORA	RAR-related orphan receptor A	15q22.2	Cholesterol receptor with potentially interactions with ROBO1 and the ARMS2 locus. RORA Regulates a number of lipid metabolism-related genes such as apolipoproteins AI,APOA5, CIII, CYP71 and PPARgamma	(Schaumberg et al., 2010; Silveira et al., 2010)
ADIPOR1	Adiponectin receptor 1	1q32.1	One of two receptors for adiponection that regulates glucose, lipid and energy metabolism	(Kaarniranta et al., 2012)

Table 5

Other genes implicated with AMD based on case-control association studies

Gene	Name	Ensemble cytogenetic band	"Known" Function (based on Entrez gene summary and UniProtKB/Swiss-Prot summary)	Reference
MYRIP	Myosin VIIA and Rab interacting protein	3p22.1	Rab effector protein involved in melanosome transport. Serves as link between melanosome-bound RAB27A and the motor proteins MYO5A and MYO7A.	(Kopplin et al., 2010)
CACNG3	Calcium channel, voltage-dependent, gamma subunit 3	16p12.1	Regulates the trafficking and gating properties of AMPA-selective glutamate receptors (AMPARs)	(Spencer et al., 2011b)
IGF1R	IGF binding protein 1	15q26.3	This receptor has high affinity binding for insulin-like growth factor. The receptor plays a critical role in cellular proliferation and survival.	(Chiu et al., 2011)
B3GALTL	Beta 1,3 galactosyltransferase-like	13q12.3	The protein encoded by this gene is a beta-1,3-glucosyltransferase that transfers glucose to O-linked fucosylglycans on thrombospondin type-1 repeats (TSRs) of several proteins.	AMD gene consortium*
ADAMTS9	ADAM metallopeptidase with thrombospondin type 1 motif, 9	3p14.1	A member of the ADAMTS (a disintegrin and metalloproteinase with thrombospondin motifs) protein family. Implicated in the cleavage of proteoglycans and the inhibition of angiogenesis	AMD gene consortium*
RAD51B	RAD51 homolog B (S. cerevisiae)	14q24.1	The protein encoded by this gene is a member of the RAD51 protein family. RAD51 family members are evolutionarily conserved proteins essential for DNA repair by homologous recombination.	AMD gene consortium*
TNFRSF10A	Tumor necrosis factor receptor superfamily, member 10a	8p21.3	The receptor is activated by tumor necrosis factor-related apoptosis inducing ligand (TNFSF10/TRAIL), and activates a death-inducing signaling complex (DISC) using caspase-8 proteolytic activation of the caspase cascade that causes apoptosis.	AMD gene consortium*
IER3	Immediate early response 3	6p21.33	The gene product functions in the protection of cells from Fas- or tumor necrosis factor type alpha-induced apoptosis. In close proximity with DDR1 thus the AMD- SNP could be associated with either gene.	AMD gene consortium*
DDR1	Discoidin domain receptor 1	6p21.33	The protein belongs to a subfamily of tyrosine kinase receptors with homology to Dictyostelium discoideum protein discoidin I in their extracellular domain. The receptor is activated by several types of collagen. In close proximity with	AMD gene consortium*

Gene	Name	Ensemble cytogenetic band	"Known" Function (based on Entrez gene summary and UniProtKB/Swiss-Prot summary)	Reference
			IER3, thus the AMD- SNP could be associated with either gene.	
COL15A1	Collagen, type XV, alpha 1	**9q22.33**	Alpha chain of type XV collagen, a member of the FACIT collagen family (fibril-associated collagens with interrupted helices). Type XV collagen strongest expression in basement membrane zones and thought to play a role in microvessel stability. Similar to COL18A1 that is cleaved to generate endostatin, a potent inhibitor of angiogenesis. In close proximity with TGFBR1 thus the AMD- SNP could be associated with either gene.	AMD gene consortium*
TGFBR1	Transforming growth factor, beta receptor 1	**9q22.33**	The serine/threonine protein kinase forms a heteromeric complex with type II TGF-beta receptors and transduces the TGF-beta signal from the cell surface to the cytoplasm. In close proximity with COL15A1 thus the AMD- SNP could be associated with either gene.	AMD gene consortium*