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Genetic risk, ethnic variations and pharmacogenetic biomarkers in age-related macular degeneration and polypoidal choroidal vasculopathy

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Introduction

Age-related macular degeneration (AMD) is the leading cause of irreversible visual impairment and blindness in older adults, affecting 1.75 million individuals in the United States alone and projected to increase 50% by 2020 due to an aging population [1,2]. AMD typically peaks around age 80 and the prevalence increases with age. Though the exact etiology of AMD remains unknown, evidence has suggested that age, smoking, and genetics are key predisposition factors for AMD susceptibility [3,4]. Genome-wide association studies (GWAS), in which millions of single-nucleotide polymorphisms (SNPs) are tested against a trait of interest, have revolutionized the concept of molecular genetics for common complex disorders in ophthalmology. Since 2005, with the initial successful discovery that variants in the complement factor H (*CFH*) gene confers a 7.4-fold increased likelihood of late AMD, more than 1600 publications from approximately 250 diseases and traits have been reported [5].

In the last few years, there is increasing evidence of ethnic differences in the epidemiology, risk factors, clinical presentation and manifestation of AMD [6]. For example, polypoidal choroidal vasculopathy (PCV) has been suggested to be a variant of AMD. Although phenotypically very similar to AMD, PCV has a very different natural history, treatment response to anti-vascular endothelial growth factor (anti-VEGF) agents and photodynamic therapy, and marked ethnic differences in disease prevalence. PCV could occur at any age between the 20s and 80s, but is commonly diagnosed around age 65, one decade younger

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than AMD [7]. It is more frequent in blacks and Asians and is responsible for over 20-50% of neovascular AMD in Asians, compared to 4-10% in Caucasians [7,8]. Despite these differences, there is supporting evidence, particularly from a genetic perspective, that links these two disease entities, resulting in the continual debate as to whether PCV and AMD are different diseases or whether PCV is part of the disease spectrum of AMD. In this review, we compare and contrast AMD and PCV with particular reference to ethnic variation, disease risk assessment and potential for pharmacogenetic interventions.

Age-related macular degeneration

AMD is a leading cause of visual impairment and blindness in older adults with a high genetic predisposition. Earlier reports of familial aggregation studies [9-11], twin studies [12,13], and linkage studies [14,15] have demonstrated strong evidence of a genetic contribution in the etiology of AMD. However, certain presentations of AMD pose challenges in identifying specific causative genes. First, the prevalence of AMD peaks around the eighth decade, leaving only one generation of subjects to be studied. Parents of the proband are often deceased and children of the proband are often not yet affected [3]. In addition, the phenotypic heterogeneity of AMD with different phenotypes makes it difficult to find the causative genes or regions [3]. Moreover, AMD is a common complex disorder with complex inheritance patterns due to various gene and environmental interactions. Yet, despite these challenges, AMD represents an unusual example of the “common disease-common variant” theory in which several variants identified on the *CFH* gene have relatively large effects on disease outcome [16]. Even though the most well-established and consistent association of AMD is observed with complement factor H (*CFH*) on chromosome 1, recent studies have also shown that other candidate genes in the complement pathway, *ARMS2/HTRA1* on chromosome 10q26, *LIPC*, *CETP*, and *TIMP2* are also susceptible loci associated with AMD [4].

Genetic Risk Factors and Disease Risk Assessment

CFH and the complement pathway—In 2005, three independent research groups identified a common coding variant, Y402H (rs1061170), in the *CFH* gene on chromosome 1 that was strongly associated with susceptibility of AMD, with reported odds ratio (OR) ranging from 2.5 to 3.3 for all AMD and as high as 7.4 for advanced AMD [16-18]. The Y402H variant, resulting in a tyrosine-to-histidine substitution, was the first and most significant SNP associated with AMD risk identified through GWAS. Since then, this finding was consistently replicated in many independent studies of Caucasian [3,16-24], Hispanics [22] and in some cohorts of Asian ancestry [25-28]. However, it was not replicated in other Asian [22,29,30] or Hispanic [31] studies (**Table 1**). Ethnic variation in the frequency of the C risk allele at Y402H does not correlate with the trend of AMD prevalence in various ethnic populations, suggesting that other susceptible genes are important in AMD and that these polymorphisms may be population-specific [22,32]. For example, the frequency of early AMD in the Japanese is half that of the Caucasians (12.7% vs. 28%) and the frequency of late AMD is also half that of the Caucasians (0.87% vs. 1.7%). However, the frequency of the C risk allele of the Y402H polymorphism is disproportionately much lower in the Japanese compared to the Caucasians (7% vs. 34%)

[32,33]. In other ethnicities, the frequency of the C risk allele at Y402H is similar in African-Americans compared to Caucasians (35% vs. 34%); yet, the prevalence of late AMD is about five-folds lower in African-Americans compared to Caucasians [1,32,34]. In another prospective population study examining individuals without cardiovascular diseases, Multi-Ethnic Study of Atherosclerosis (MESA) found that subjects with the *CFH* Y402H CC compared to the TT genotype had the highest frequency of early AMD in whites, blacks, and Hispanics, but not in the Chinese. The variation of *CFH* did partially explain some of the observed difference in the prevalence of AMD in Hispanics and Chinese versus whites, but did not account for the difference observed between the whites and blacks [22].

The association of *CFH* in AMD implicated that the complement cascade plays a critical role in the development of AMD and is now also regarded as a major contributor to susceptibility of AMD. Since then, several candidate genes in the complement pathway were investigated and additional signals include variants on complement 2 (*C2*)/complement factor B (*CFB*) at 6p21 [23,24,35,36], complement 3 (*C3*) at 19p13 [24,36-38], and complement factor I (*CFI*) at 4q25 [37,39] were also identified (**Table 1**). These findings were also investigated in other ethnic populations as well [28,40-44]. Earlier studies conducted to fine-map in and around the *CFH* region demonstrated that more than 20 other variants were more strongly associated with AMD than was the Y402H coding variant, suggesting that regulation of the expression in *CFH* and its neighboring genes, rather than alterations in the coding sequence, mediates AMD susceptibility [45,46]. This analysis was soon corroborated by others [23,47], demonstrating that single genetic variant was not the only causative factor that accounted for the contribution of the *CFH* locus to disease susceptibility.

***ARMS2/HTRA1* and other susceptibility genes**—In addition to *CFH* and the complement pathway, the region at chromosome 10q26 also harbors additional signals to AMD susceptibility, namely the age-related maculopathy susceptibility 2 (*ARMS2*) and the high-temperature requirement factor H (*HTRA1*) genes. The identification of the original signals in this region came from fine-mapping of the linkage peak at 10q26 [48,49]. Subsequently, this finding was corroborated by several studies in Caucasians [23,36,50], Asians [51,52], Hispanics [53], but borderline significance in blacks [53] (**Table 1**). The Population Architecture using Genomics and Epidemiology (PAGE) Study found that the non-synonymous coding variant of T allele at rs10490924 (A69S) increases AMD susceptibility in the Caucasians and Hispanics, after adjusting for age, sex, smoking, and *CFH* Y402H (OR=2.10, p=0.001 for Caucasians and OR=2.45, p=0.032 for Hispanics); however, the direction of effect was opposite in the blacks and only marginally significant (OR=0.41, p=0.052) [53].

The identity of the gene that affects disease susceptibility is still controversial, with two earlier reports suggesting *HTRA1* as a candidate of AMD susceptibility [50,51]. However, more recent studies implicated that *ARMS2* (previously, the hypothetical LOC387715) is a stronger candidate [49,54,55], which as been shown to mediate mRNA turnover [54]. It is also possible that susceptible variants within *ARMS2* modulate the promoter activity of *HTRA1*, so that both *ARMS2/HTRA1* contribute to AMD susceptibility [46]. In one European study, the SNP rs11200638 at the promoter region of *HTRA1* confers a 49.3%

population attributable risk and the risk allele was associated with an elevated mRNA and protein expression and level of *HTRA1* [50]. The risk allele of the same SNP was highly significant in the Chinese and has 10 times the risk of developing AMD compared to subjects with the wild-type allele [51]. Additional investigations are necessary to define the role of *ARMS2/HTRA1* and associated causal variants in AMD pathogenesis.

Association studies as to genes in the HDL cholesterol pathway have also been implicated with AMD, including *LIPC*, *CETP*, *ABCA1* and *LPL* [24,37,56,57], but not *ABCA4* [3]. The *APOE* gene has also been linked to AMD [3,58-60]; furthermore, it has been demonstrated that both $\epsilon 2$ and $\epsilon 4$ are associated with AMD (OR=1.83, P=0.04 for $\epsilon 2$; OR=0.72, P=4.4 $\times 10^{-11}$ for $\epsilon 4$), with $\epsilon 2$ increasing risk and $\epsilon 4$ decreasing risk [60]. Genes in the collagen matrix pathway, *COL10A1* and *COL8A1* [24], the extracellular matrix pathway, *TIMP3* [24,37], the angiogenesis pathway, *VEGF* [3,24], also show association with AMD. Other genes, such as those involved with inflammation and immunity, *TLR3* [61] and *SOD2* [62], and the 9p21 region [63] did not show an association with AMD. In recent years, meta-analyses demonstrated that the *REST-C4orf14-POLR2B-IGFBP7* at 4q21 does not show an association with AMD, while the T allele at rs13278062 of *TNFRSF10A-LOC389641* at 8p21 decreases risk of AMD [26,64] (**Table 1**).

Pharmacogenetic Biomarkers

Photodynamic Therapy in AMD—One of the treatments for neovascular AMD involves the use of photodynamic therapy (PDT) with verteporfin (Visudyne, Novartis, Basel, Switzerland), where a photosensitizing dye is injected intravenously, followed by phototherapy to generate oxygen-free radicals that target the pathological vessels. Several studies have examined the association of an individual's genotypic variation with PDT treatment, particularly of the variants on *CFH*, *ARMS2/HTRA1*, and other candidate genes (**Table 2**). The earliest pharmacogenetic study of Y402H and response to PDT was a small case series of 27 Caucasian subjects. Almost half of the patients with the CC or CT risk genotype lost more than 15 letters after PDT treatment. Furthermore, this study suggests that patients who are heterozygous with the CT genotype lost a median of 3.5 letters, compared to the median loss of 12 letters in the homozygous risk CC group, indicating that the number of risk allele correlates with PDT treatment response in a step-wise fashion. The sample size of the TT group was too small to be statistically conclusive [65]. Another study of Caucasian population found that visual acuity of the TT genotype group was significantly worse than that of the TC or CC genotype after PDT treatment [66]. Other larger studies of Caucasian populations, however, found no association of the Y402H polymorphism to PDT treatment outcome [67-69]. Interestingly, in the Asian populations, subjects with the Y402H polymorphism of *CFH* also showed no association with PDT response, but other SNPs (rs1410996 and rs2274700) of *CFH* did show a reduction of recurrence after PDT treatment in a study of 110 Japanese subjects [70].

Studies that examined the variants in *ARMS2/HTRA1* have found no association with PDT treatment in the Caucasian populations [66,71], but the GG genotype of rs11200638 in *HTRA1* was associated with visual improvement and less recurrence after PDT treatment in the Japanese [70]. Furthermore, there was a significant association between a more

favorable PDT response to two C-reactive protein (*CRP*) polymorphisms with homozygous alleles GG at rs2808635 (GG; OR=3.92; $p=0.048$) and AA at rs877538 (AA; OR=6.49; $p=0.048$) [69]. Other genes, such as those related to angiogenesis, were also examined. Two VEGF polymorphisms, rs699947 and rs2146323, were significantly associated with PDT treatment response, while another polymorphism rs3025033 did not. The allele frequency of rs699947 for AA, AC, and CC were 14%, 39%, and 46% in non-responders versus 40%, 48%, and 12% in responders, respectively ($p=0.0008$). The allele frequency of rs2146323 for AA, AC, and CC were 4%, 32%, and 64% in non-responders versus 24%, 38%, and 38% in responders, respectively ($p=0.0369$). Thus, the C allele in both SNPs in *VEGF* were associated with a higher rate of non-responder to PDT ($p=0.0003$ for rs699947 and $p=0.0036$ for rs2146323) [72]. In the Japanese population, polymorphisms (rs699947, rs1570360, and rs2010963) in the *VEGF* gene were not associated with PDT treatment [70].

Other studies have examined candidate genes in the coagulation pathway, including factor V (G1691A), prothrombin (G20210A), factor XIII-A (G185T), MTHFR (C677A), methionine synthase (A2756G), and methionine synthase reductase (A66G), and its relationship to PDT response. In classic choroidal neovascularization (CNV), prothrombin (G20210A) and MTHFR (C677A) were significantly associated with PDT responders, while factor XIII-A (G185T) was significantly associated with PDT non-responders [73]. In occult CNV, prothrombin (G20210A) and factor V (G1691A) were significantly associated with PDT responders, while factor XIII-A (G185T) was significantly associated with PDT non-responders. Furthermore, MTHFR, methionine synthase, or methionine synthase reductase were not associated with PDT response in occult CNV patients [74] (**Table 2**).

Anti-VEGF therapeutics in AMD—Anti-VEGF therapies are now regarded as the standard of care in the treatment of neovascular AMD. Two of the most widely-use treatments are ranibizumab and bevacizumab. Ranibizumab (Lucentis, Genentech), a FDA-approved anti-VEGF therapy for AMD, is a recombinant, fragmented, monoclonal antibody that binds to VEGF. On the other hand, bevacizumab, (Avastin, Genentech), though not U.S. FDA-approved for ocular treatment, is a full-length monoclonal antibody derived from the same parent mouse antibody with similar function as that of ranibizumab but with a fraction of the cost. Bevacizumab, FDA-approved for metastatic colon cancer, is given as an off-label treatment for ocular angiogenic disorders. An individual's genetic variation may affect the treatment response in both of these drugs.

For the Y402H *CFH*, patients with the TC and TT genotype show more than 5-fold improvement in visual outcome compared to the CC genotype after bevacizumab treatment ($p=0.004$) [75]. On average, visual acuity improved from 20/248 to 20/166 for the TT genotype, improved from 20/206 to 20/170 for the TC genotype, but decreased from 20/206 to 20/341 for the CC genotype ($p=0.016$) [75]. This finding was confirmed in a prospective study with twice the number of subjects, where the risk CC genotype was associated with a worse visual outcome. The percentage of visual acuity loss of 3 or more lines after bevacizumab treatment were 41%, 26%, and 28% in CC, CT, and TT genotypes ($p=0.04$) [76]. In the Chinese, one study found that the mean visual acuity change at rs800292 of *CFH* was 4.4, 8.7, and 15.5 letters for CC, CT, and TT genotypes, respectively, after bevacizumab [77].

In similar experiments with ranibizumab, patients with the TC and TT genotypes for *CFH* required fewer injections over a nine-month period. On average, patients with the TT genotype required 3.3 injections compared to 3.9 and 3.8 for CC and TC genotypes to achieve complete resolution. The same study found that patients with the risk CC allele were 37% more likely to require re-injections ($p=0.04$) [78]. This finding was confirmed in other studies that also showed patients with the risk CC genotype had less visual improvement or were poor responders after ranibizumab treatment [79-81]. Furthermore, a meta-analysis demonstrated that rs1061170 at *CFH* was a predictor of treatment response, especially for anti-VEGF therapies [82]. However, other studies also found the risk genotypes at Y402H of *CFH* had a more favorable outcome [83] or did not show a pharmacogenetic response with either intravitreal ranibizumab [84,85] or with bevacizumab [85].

In the case of *ARMS2/HTRA1*, most studies found no statistical difference between the polymorphisms in *ARMS2/HTRA1* with treatment response in either anti-VEGF therapies [75,80,83-85], with the exception of two studies showing a worse visual improvement in subjects with the homozygous TT risk allele at rs10490924 (A69S) after ranibizumab [79] or bevacizumab [77] injections. Other candidate gene studies found that patients with the risk genotype (CC) at rs1413711 of *VEGF* has a more significant visual gain after ranibizumab [83], the G allele at rs699946 of *VEGF* was significantly associated with a better visual prognosis after either intravitreal bevacizumab or triple therapy (PDT with intravitreal bevacizumab and triamcinolone acetonide) [86], and patients with the *APOE* ϵ 4 allele have an improved outcome compared to the ϵ 2 allele at 3 month follow-up ($p=0.02$) but not at 12 month ($p=0.06$) after either anti-VEGF treatment [87].

In a study examining the cumulative effect of risk alleles at *CFH* (Y402H; rs1061170), *ARMS2* (A69S; rs10490924), *VEGF* (rs699947 and rs833069), *KDR* (rs2071559 and rs7671745), *LPR5* (rs3736228), and *FZD4* (rs10898563) after ranibizumab treatment, subjects without the high-risk alleles in *CFH* and *ARMS2* have significantly more visual improvement compared to subjects with the high-risk alleles ($p=0.009$). The mean visual acuity improvement was 10 letters in subjects without the 4-risk alleles, compared to no improvement in subjects with all 4-risk alleles. By adding *VEGF* into the model, they found that subjects with all 6-risk alleles in *CFH*, *ARMS2*, and *VEGF* demonstrated a mean loss of 10 letters after ranibizumab treatment, whereas the other allele groups all demonstrated improvement ($p<0.0001$), suggesting a cumulative effect of the risk alleles with a poorer response rate to treatment [88].

Vitamins in AMD—In the Age-Related Eye Disease Study (AREDS), a subset of 876 participants of European descent was evaluated for a pharmacogenetic response of the AREDS vitamins with antioxidants and zinc to polymorphisms in *CFH* (Y402H) and *ARMS2/HTRA1* (A69S). They found that subjects with the TT genotype at Y402H had a more favorable outcome compared to the CC genotype after treatment. The reduction in AMD progression was seen in 68% of subjects with the TT genotype compared to 11% with the high-risk CC genotype. No significant association was observed for A69S in *ARMS2/HTRA1* [89] (**Table 2**).

Polypoidal choroidal vasculopathy

Reported thirty years ago was the original clinical description of PCV as an abnormal subretinal exudative and hemorrhagic disorder in the posterior pole [7]. Since then, with the advent and clinical utility of indocyanine green angiography (ICGA), numerous reports have characterized PCV as a disease with polypoidal, branching network in the inner choroid. Similar to AMD, the etiology of PCV remains largely unknown. The phenotypic similarities between neovascular AMD and PCV have led to the assumption that PCV may be a subset of neovascular AMD that is more prevalent in blacks and Asians. However, differences in natural history, treatment response as well as ethnic prevalence have resulted in continual controversy as to whether to group or distinguish these two entities. The two most well established genetic loci associated with AMD are *CFH* and *ARMS2/HTRA1*, and their associations as well as treatment response in PCV are described below.

Disease Risk Assessment

The strongest association of AMD in *CFH* gene was through SNP rs1061170 (Y402H); yet this variant was shown to associate with PCV in only a small sample of Caucasian population [90], and in some [91] but not other Japanese populations [92] (**Table 1**). This discrepancy could be due to an intrinsic ethnic difference in the frequency of the C risk allele, similarly to that seen in AMD studies of Asian population, where the frequency of the C allele is rather rare in Asian populations [22,32]. Using a haplotype-tagging approach in the *CFH* region, rs800292 (I62V), another variant on *CFH*, was found to be more significantly associated with PCV in some studies [91,92], but not others [93].

A comprehensive meta-analysis found variants at *ARMS2/HTRA1* (rs10490924, OR=2.27, $p<0.00001$; rs11200638, OR=2.72, $p<0.00001$), *CFH* (rs1061170, OR=1.72, $p<0.00001$; rs800292, OR=2.10, $p<0.00001$) or the complement pathway (*C2*; rs547154, OR=0.56, $p=0.01$) were significantly associated with PCV, with higher odds ratio observed at variants in *ARMS2/HTRA1* [94]. The strong association of *ARMS2/HTRA1* to PCV was supported by numerous studies of Asian populations [52,91,93-98]. One study, examining 243 Japanese individuals (76 PCV, 73 neovascular AMD, and 94 controls), found that both SNPs rs10490924 and rs11200638 within the *ARMS2/HTRA1* region were significantly associated with both AMD and PCV. Homozygotes for the at-risk allele (AA) had a 6.3-fold and 13.8-fold increased risk for PCV and neovascular AMD respectively, compared to homozygotes for the wild type allele (GG) at rs11200638 [52]. Similarly, both rs10490924 and rs11200638 were also significantly associated with PCV in a Chinese study, with the homozygous risk genotypes (AA for rs11200638 and TT for rs10490924) both conferring a 4.9-fold increased risk for PCV compared to wild-type genotype [96]. This finding was corroborated by another study of 109 Japanese subjects with PCV versus 85 controls, where homozygotes for the at-risk allele (TT) at rs10490924 showed a 8.4-fold increase for PCV compared to 4.0-fold increase in heterozygotes (GT), compared to wild type allele (GG) [95]. Furthermore, the frequency of the risk TT genotype at rs10490924 was seen in 89% of PCV subjects with vitreous hemorrhage, an indication of severe clinical phenotype, compared to 37% of PCV subjects without vitreous hemorrhage [95]. A few years later, the same study group with twice the number of PCV patients found that the T risk allele of

rs10490924 in *ARMS2/HTRA1* was 12 times more likely to occur in hemorrhagic pigment epithelial detachment ($p=0.0001$), have an earlier onset ($p=0.026$), and have a bilateral involvement ($p=0.007$), indicating a clinically more severe phenotype in subjects with the homozygous risk genotype [93]. When comparing PCV to neovascular AMD, only variants rs10490924 of *ARMS2/HTRA1* potentially implicate a genetic and biological difference in these two disease entities [94].

The non-synonymous SNP rs10490924 (A69S) within *ARMS2* and rs11200638 within *HTRA1* at 10q26 have been tested for disease susceptibility for both AMD and PCV. Due to a strong linkage disequilibrium across this region, it is difficult to genetically distinguish between these two susceptible candidates and prioritize of their importance toward disease pathogenesis [99]. Other studies have also examined the association of *C2/CFB* [90,92,96,100], *SERPING1* [101,102], *ELN* [103-105], *PEDF* [106-108], *APOE* [59], *SOD2* [62], *TLR3* [61], the *9p21* region [63], *RDBP* [100], *SKIV2L* [100], and *C3* [98] with PCV in different ethnicities, but meta-analysis shows that the results of these associations are inconclusive and sometimes underpowered [94]. A recent study demonstrated that *REST-C4orf14-POLR2B-IGFBP7* at 4q21 did not show an association with PCV; however, the T allele at rs13278062 of *TNFRSF10ALOC389641* at 8p21 decreases risk of PCV. Both of these observations were similar to that found for AMD [64] (**Table 1**). Despite these efforts to find genes associated with PCV, there has been no GWAS study on PCV to date.

Pharmacogenetic Biomarkers

Photodynamic Therapy in PCV—PDT with verteporfin has proved efficacious for patients with PCV in several reports [7,99]. There is also supporting evidence that PDT is more effective for the treatment of PCV compared to AMD [99,109]. One Japanese study found that visual improvement was seen in 25% of patients with PCV compared to 6% in AMD after PDT treatment, and the angiographic leakage stopped in 86% of patients with PCV compared to 61% in AMD after 1 year of follow-up [110]. This favorable outcome in PCV was confirmed in another Japanese study [111]. In terms of pharmacogenetic biomarkers of PDT in PCV, one study found that variant at the A69S (rs10490924) of *ARMS1/HTRA1* was a useful predictor for PDT treatment response as well as prognosis. Patients with the T risk allele had worse visual outcome at 12-month follow-up and were more frequently observed with recurrence [112]. However, in another study examining 638 SNPs from 42 susceptible AMD genes and its relation to PDT treatment response in PCV, only 6 SNPs from 4 genes were significant, of which rs12603825 in *SERPINF1* of the Pigment-Epithelium-Derived Factor (*PEDF*) was significantly associated with retreatment-free period ($p=0.01$) in 3 additional independent cohort. Subjects with the minor A allele received additional PDT treatment in a shorter time period ($p=0.0038$) that remained significant after correcting for multiple testing ($p=0.015$) and had worse visual prognosis. Smoking status was not significantly correlated in this model [108] (**Table 2**).

There is also supporting evidence that PDT is more effective than anti-VEGF therapies for the treatment of PCV [109,113]. PDT is now regarded as the first treatment choice for PCV [7,99]. Despite this, expansion in lesion size, subretinal hemorrhage, recurrence, development of new polypoidal lesions, and choroidal atrophy are several of the possible

complications after PDT treatment in PCV and should be cautiously monitored [7,99]. Furthermore, recent studies have demonstrated the utility of argon laser for the treatment of extrafoveal PCV and may be an alternative treatment for this subset of PCV patients [114].

Anti-VEGF therapies in PCV—Anti-VEGF therapies have been regarded as the current standard of care for AMD, but its utility and efficacy for PCV still warrants further investigation. One study found no difference in the genetic variation at *CFH* (Y402H and I62V) and *ARMS2/HTRA1* (A69S) to intravitreal ranibizumab treatment after 12 month of follow-up in the Japanese [84]. Another study examining the combination therapy of PDT with intravitreal bevacizumab injection in PCV of Koreans found that the risk genotypes, TT of rs10490924 and AA of rs11200638 at *ARMS2/HTRA1*, had significantly poorer outcome after 1 year of follow-up [115]. On average, subjects with the TT genotype at rs10490924 had significantly less absence of leakage ($p=0.04$), less polyp regression ($p=0.006$), and worse visual acuity ($p=0.034$) at 12-month follow-up. This was similar for the AA genotype at rs11200638, with significantly less absence of leakage ($p=0.019$), less polyp regression ($p=0.002$), and worse visual acuity ($p=0.022$) at 12-month follow-up. The intermediate risk phenotypes also had an intermediate outcome after combined PDT and bevacizumab injection [115].

Future Directions

The success of identifying the genetic risk factors for AMD has spawned a niche focused on determining the genetic components of PCV to determine if the differences in clinical phenotype can be correlated with differences in genotype. Even though PCV and AMD appear to be clinically distinct, there is evidence to suggest that these two conditions share common genetic determinants. The disease risk assessment and pharmacogenetics of PDT or anti-VEGF therapies prove useful in these conditions, but the data are sometimes conflicting. No definite conclusion can be drawn at this time due to small sample size, too few studies of other ethnicity, and different study designs. There needs to be more studies conducted to find population-specific signals to detect pharmacokinetics and pharmacogenetics tailored to each ethnicity, especially in Asian ethnicities where PCV is more prevalent. With advances in massively parallel next-generation sequencing and decreased cost of such technologies, investigators will be able to more thoroughly assess rare variants and their contribution to disease susceptibility. The re-sequencing of associated genomic regions found from Caucasian studies GWAS can be conducted in other ethnicities, especially Asian cohorts. As with many population genetics and pharmacogenetics studies to date, more follow-up functional studies to verify the roles of the identified variants are crucial to establish causality. Other epigenetic studies, for example, in transcriptomics taking into account differential gene expression as well as gene-gene and gene-environment interactions will also have to be conducted. For true translation into patient practice, large well-designed randomized clinical trials will also have to be implemented. Changes in the management of AMD or PCV will continue to progress as the contribution from genetics and pharmacogenetics studies continue to accumulate over the next 5-10 years, contributing to the evolution to individualized medicine. Currently, however, the field still faces many challenges to the clinical implementation of personalized medicine, which should deliver a

risk score and response to targeted therapeutics stratified by ethnicity with high confidence that is clinically actionable.

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Table 1

Disease risk assessment in age-related macular degeneration (AMD) and polypoidal choroidal vasculopathy (PCV)

Disease	Region	Gene	Ethnicity	Risk assessment	References
AMD	1p22	<i>ABCA4</i>	Caucasians, Asians	Inconsistent results	[3]
	1q32	<i>CFH</i>	Caucasians	C allele of Y402H (rs1061170) increases risk	[3,16-24]
			Asians	Inconsistent results for rs1061170 (Y402H) but rs800292 (I62V) more significant in Asians	[22,25-30]
			Hispanics	Inconsistent results for Y402H	[22,31]
			Blacks	Trend and prevalence of CC allele of Y402H higher in early AMD; *	[22]
	3q12	<i>COL8A1</i>	Caucasians	C allele at rs13095226 increases risk	[24]
	4q12	<i>REST-C4orf14-POLR2B-IGFBP7</i>	Asians	G allele at rs1713985 increases risk, but insignificant in meta-analysis study *	[26,64]
	4q25	<i>CFI</i>	Caucasians	C allele at rs10033900 and rs2285714 decreases risk	[37,39]
	4q35	<i>TLR3</i>	Asians	No association at rs3775291	[61]
	6p12	<i>VEGF</i>	Caucasians	T allele at rs4711751 increases risk	[3,24]
	6p21	<i>C2/CFB</i>	Caucasians	Minor alleles at rs9332739 (C2), rs547154 (C2), rs4151667 (CFB), and rs641153 (CFB) decrease risk	[23,24,35,36]
			Asians	Minor alleles at rs9332739 (C2), rs547154 (C2), rs4151667 (CFB), and rs641153 (CFB) decrease risk; *	[28,40-42]
	6q21-q22.3	<i>COL10A1/FRK</i>	Caucasians	T allele at rs1999930 decreases risk	[24]
	6q25	<i>SOD2</i>	Asians	No association at rs4880	[62]
	8p21	<i>LPL</i>	Caucasians	G allele at rs12678919 increases risk	[37]
	8p21	<i>TNFRSF10A-LOC389641</i>	Asians	T allele at rs13278062 decreases risk	[26,64]
	9p21	<i>9p21</i>	Asians	No association at rs10757278 or rs1333040	[63]
	9q31	<i>ABCA1</i>	Caucasians	T allele at rs1883025 decreases risk	[37,56,57]
	10q26	<i>ARMS2/HTRA1</i>	Caucasians	T allele at rs10490924 and A allele at rs11200638 increase risk	[23,36,50]
			Asians	T allele at rs10490924 and A allele at rs11200638 increase risk	[51,52]

Disease	Region	Gene	Ethnicity	Risk assessment	References
			Hispanics	T allele at rs10490924 increases risk	[53]
			Blacks	Borderline significance * ; T allele at rs10490924 decreases risk (opposite direction of effect compared to other ethnicities)	[53]
	15q22	<i>LIPC</i>	Caucasians	T allele at rs10468017 and rs493258 decrease risk.	[37,56,57]
	16q21	<i>CETP</i>	Caucasians	A allele at rs3764261 increase risk	[24,37]
	19p13	<i>C3</i>	Caucasians	Meta-analysis shows G allele at rs2230199 and A allele at rs1047286 increase risk	[24,36-38]
			Asians	Inconsistent finding	[28,42-44]
	19q13	<i>APOE</i>	Caucasians, Asian, Hispanics, blacks	Inconsistent results, but e4 allele seems to be protective while e2 increases risk; another study found both e2 and e4 are less prevalent in Asian AMD.	[3,58-60]
	22q12	<i>TIMP3</i>	Caucasians	A allele of rs9621532 increase risk	[24,37]
PCV	1q32	<i>CFH</i>	Caucasians	C allele of Y402H (rs1061170) increases risk	[90,94]
			Asians	Inconsistent results for rs1061170 (Y402H) and rs800292 (I62V)	[91-94]
	4q12	<i>REST-C4orf14-POLR2B-IGFBP7</i>	Asians	No association at rs1713985	[64]
	4q35	<i>TLR3</i>	Asians	No association at rs3775291	[61]
	6p21	<i>C2/CFB</i>	Asians and Caucasians	Minor alleles at rs547154 (<i>C2</i>) and rs4151667 (<i>CFB</i>) decrease risk; *	[90,92,94,96,100]
	6p21	<i>RBDP-SKIV2L</i>	Asians	C allele at rs3880457 and rs2075702 decrease risk	[100]
	6q25	<i>SOD2</i>	Asians	No association at rs4880	[62]
	7q11	<i>ELN</i>	Asians and Caucasians	Inconsistent results (rs2301995)	[94,103-105]
	8p21	<i>TNFRSF10A-LOC389641</i>	Asians	T allele at rs13278062 decreases risk	[64]
	9p21	<i>9p21</i>	Asians	A allele at rs10757278 increases risk; no association at rs1333040	[63]
	10q26	<i>ARMS2/HTRA1</i>	Asians	T allele at rs10490924 and A allele at rs11200638 increase risk	[52,91,93-98]
	11q12	<i>SERPING1</i>	Asians	Inconsistent results (rs2511989)	[94,101,102]
	17p13	<i>PEDF</i>	Asians	Inconsistent results (rs1136287)	[94,106-108]
	19p13	<i>C3</i>	Asians	G allele of rs2241394 increases risk	[98]
	19q13	<i>APOE</i>	Asians	No association, but e2 and e4 are less prevalent in PCV	[59]

* Some results did not reach statistical significance

Table 2

Pharmacogenetic/pharmacogenomic biomarkers of clinical outcomes in AMD and PCV

Disease	Treatment	Gene	Variant	Ethnicity	Response	References
AMD	Photodynamic therapy	CFH	Y402H	Caucasian	CC lost 12 letters; CT lost 3.5 letters.	[65]
				Caucasian	TT genotype had worse visual acuity compared to TC or CC.	[66]
				Caucasians, Asians	No association	[67-70]
			rs1410996, rs2274700	Asians	Improvement	[70]
		ARMS2/HTRA1	A69S	Caucasians	No association	[66,71]
			rs11200638	Asians	GG genotype had visual improvement and less recurrence	[70]
		VEGF	rs699947	Caucasians	Higher rate of non-responder with C allele	[72]
				Asian	No association	[70]
			rs2146323	Caucasians	Higher rate of non-responder with C allele	[72]
			rs3025033	Caucasians	No association	[72]
			rs1570360	Asian	No association	[70]
			rs2010963	Asian	No association	[70]
		CRP	rs2808635	Caucasians	Favorable response to PDT with GG genotype	[69]
			rs877538	Caucasians	Favorable response to PDT with AA genotype	[69]
		Factor V	G1691A	Caucasians	Associated with PDT responder in occult CNV	[74]
		Prothrombin	G2010A	Caucasians	Associated with PDT responder in classic and occult CNV	[73,74]
		Factor XIII-A	G185T	Caucasians	Associated with PDT non-responder in classic and occult CNV	[73,74]

Disease	Treatment	Gene	Variant	Ethnicity	Response	References
		<i>MTHFR</i>	C677A	Caucasians	Associated with PDT responder in classic CNV; no association in occult CNV	[73,74]
		<i>Methionine synthase</i>	A2756G	Caucasians	No association in occult CNV	[74]
		<i>Methionine synthase reductase</i>	A66G	Caucasians	No association in occult CNV	[74]
	Anti-VEGF	<i>CFH</i>	Y402H	Caucasians	CC genotype had worst visual improvement; required more re-injections	[75,76,78-82]
				Caucasians	CC genotype had favorable outcome	[83]
				Caucasians, Asians	No association	[84,85]
			rs800292	Asians	CC genotype had worst visual improvement	[77]
		<i>ARMS2/HTRA1</i>	A69S, rs11200638	Caucasians, Asians	No association	[75,80,83-85]
			A69S	Caucasians, Asians	TT genotype had worst visual outcome	[77,79]
		<i>VEGF</i>	rs1413711	Caucasians	Risk CC genotype had more visual improvement	[83]
			rs699946	Asians	G allele had better outcome	[86]
		<i>APOE4</i>	ε4	Caucasians	Improvement at 3 month but not 12 month	[87]
		<i>CFH+ARMS2+VEGF</i>	rs1061170, rs10490924, rs699947	Caucasians	Poor response with cumulative risk alleles	[88]
	Triple therapy	<i>VEGF</i>	rs699946	Asians	G allele had better outcome	[86]
	AREDS vitamins	<i>CFH</i>	Y402H	Caucasians	TT genotype had better outcome	[89]
		<i>ARMS2/HTRA1</i>	A69S	Caucasians	No association	[89]
PCV	Photodynamic therapy	<i>CFH</i>	Y402H	Asians	No association	[108]
		<i>ARMS2/HTRA1</i>	A69S	Asians	T risk allele had worse visual outcome; one study found no association.	[108,112]

Disease	Treatment	Gene	Variant	Ethnicity	Response	References
		<i>FBLN5</i>	rs17732513	Asians	Association with PDT response	[108]
		<i>CX3CR1</i>	rs17793056	Asians	Association with PDT response	[108]
		<i>SERPINF1/PEDF</i>	rs12603825	Asians	A genotype had worse visual prognosis	[108]
		<i>TLR4</i>	rs11536889	Asians	Association with PDT response	[108]
	Anti-VEGF	<i>CFH</i>	Y402H	Asians	No association	[84]
			I62V	Asians	No association	[84]
		<i>ARMS2/HTRA1</i>	A69S	Asians	No association	[84]
	Combination therapy	<i>ARMS2/HTRA1</i>	A69S, rs11200638	Asians	TT of rs10490924 and AA of rs11200638 had worse visual prognosis	[115]

Note: Y402H (rs1061170); I62V (rs800292); A69S (rs10490924)