

# Importance of genetic polymorphisms in the response to age-related macular degeneration treatment

## *Importância dos polimorfismos genéticos na resposta terapêutica da degeneração macular relacionada à idade*

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### ABSTRACT

Age-related macular degeneration (AMD) is a degenerative disorder that affects the central retina and involves the Bruch's membrane, the retinal pigment epithelium and the photoreceptors. Recent studies have shown that polymorphisms of the CFH, LOC387715 and VEGF genes are associated with AMD. Herein, we review the literature to analyze the association between the main genetic polymorphisms and the response to the existing therapeutic modalities. Patients with CFH high-risk alleles show a poorer response to preventive treatment of AMD with antioxidants and zinc. The association between genetic polymorphisms and response to photodynamic therapy and antiangiogenic drugs, however, is controversial until now.

**Keywords:** Macular degeneration/genetics; Antioxidants; Polymorphism, genetic; Treatment outcome

### RESUMO

A degeneração macular relacionada à idade (DMRI) é uma doença degenerativa que afeta a retina central e envolve a membrana de Bruch, o epitélio pigmentar da retina e os fotorreceptores. Estudos recentes têm mostrado que polimorfismos dos genes CFH, LOC387715 e VEGF estão associados com a DMRI. Neste trabalho, é feita uma revisão da literatura para análise da associação entre os principais polimorfismos genéticos e a resposta às diferentes modalidades terapêuticas existentes. Observa-se que os pacientes portadores dos alelos de risco do gene CFH apresentam uma pior resposta ao tratamento preventivo da DMRI com antioxidantes e zinco. Já a associação entre o polimorfismo genético e a resposta à terapia fotodinâmica e às drogas antiangiogênicas é, até o momento, controversa.

**Descritores:** Degeneração macular/genética; Antioxidantes; Polimorfismo genético; Resultado de tratamento

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## INTRODUÇÃO

**A**ge-related macular degeneration (AMD) is a degenerative disorder that affects the central retina and involves the Bruch's membrane, the retinal pigment epithelium (RPE) and the photoreceptors.<sup>(1,2)</sup> It is characterized by a progressive, painless loss of central vision associated with ageing. AMD is considered the leading cause of irreversible blindness and responsible for a low quality of life in the affected population.<sup>(1,3)</sup> In the United States of America population aged 40 years and older, the estimated prevalence of any AMD is 6.5%.<sup>(4)</sup> The disease is usually classified into dry and wet types, responsible for 15% and 85% of cases, respectively. In the dry form, visual loss is usually gradual and is characterized by subretinal deposits called drusen or retinal pigment epithelial (RPE) abnormalities, including hyper or hypopigmentation. Larger drusen may become confluent and evolve into drusenoid RPE detachments, which can progress to geographic atrophy and less frequently to wet AMD. Wet AMD (also called exudative or neovascular AMD) occurs when choroidal neovascular membrane grows under the RPE or between the RPE and neurosensory retina, leading to subretinal hemorrhage and subsequent scar tissue formation.<sup>(1,2)</sup>

Etiological research suggests that AMD is a complex disease, caused by the actions and interactions of multiple genes and environmental factors such as smoking and hypertension.<sup>(5,6)</sup> Recent studies have shown that some genetic polymorphisms are associated with AMD. A genetic variation in the complement factor H (CFH) gene on chromosome 1q32 is one of the most studied gene polymorphisms related to AMD. This polymorphism (rs 1061170) results in a tyrosine-to-histidine substitution at amino acid position 402 (Y402H) in the CFH protein.<sup>(7-33)</sup> The A69S polymorphism (rs 10490924) within the gene LOC387715 on chromosome 10q26 that leads to an alanine-to-serine substitution was also found to confer an increased risk for development of AMD.<sup>(33-50)</sup> Some papers suggested that the vascular endothelial growth factor (VEGF) gene could play a role in the pathogenesis of AMD.<sup>(51,58)</sup> However, many different single nucleotide polymorphisms (SNPs) were tested and limited sample sizes and diverse ethnic origin of cases and controls were studied to ensure a statistically valid conclusion. It has also been demonstrated that common CFH and LOC387715 polymorphisms were independently related to progression from early or intermediate stages to advanced forms of the disease.<sup>(59)</sup>

Herein, we review the main published studies that evaluate the response to the treatment of AMD related to genetic polymorphisms.

Klein et al. made a retrospective analysis of participants of a randomized, controlled clinical trial, the Age-Related Eye Disease Study (AREDS) to investigate the possible association between the response to oral antioxidants and zinc with genetic polymorphisms. The AREDS study enrolled 4757 participants from 11 clinical centers and established that a combination of zinc and antioxidants (B-carotene, vitamin C, and vitamin E) produced a 25% reduction in development of AMD over 5 years and a 19% reduction in severe vision loss in individuals determined to be at high risk of developing the advanced forms of the disease. A treatment interaction was observed between the CFH Y402H high-risk genotype and supplementation with antioxidants plus zinc ( $p = 0.03$ ). An interaction ( $p = 0.004$ ) was observed in the AREDS treatment groups taking zinc when compared with the groups taking no zinc, but not in groups taking antioxidants compared with those taking no antioxidants ( $p = 0.59$ ). There were no significant treatment interactions observed with LOC387715.<sup>(60)</sup>

Other authors have studied the effect of the LOC387715, CFH and VEGF genotypes on the response to photodynamic therapy (PDT) with controversial results.<sup>(61,68)</sup> Goverdhan et al. genotyped a total of 557 cases with AMD and 551 normal controls for the CFH Y402H. Twenty-seven PDT-treated patients were followed up for 15 months and individuals with different CFH genotypes were then analyzed for any association with visual change following PDT. The number of patients carrying the high-risk C allele was 70.4% in those requiring PDT as compared to 52.3% in the non-PDT group ( $p=0.011$ ), and presence of the CC genotype significantly increased the risk of PDT ( $p=0.015$ ). The degree of visual loss following PDT was significantly higher in the CFH CC genotype group ( $p=0.038$ ); 50% of CC cases and 45% of the CT cases lost 15 or more ETDRS letters at final follow-up. In conclusion, they showed that patients homozygous for the CFH high risk allele seem to have worse outcome after PDT.<sup>(61)</sup> Brantley et al. also found a potential relationship between CFH genotype and response to PDT. However, they showed that patients with the CFH TT genotype (T: non-risk allele) fared significantly worse with PDT than those with the CFH TC and CC genotypes.<sup>(62)</sup> Other studies did not show significant association between CFH polymorphism and PDT response for neovascular AMD.<sup>(63,64)</sup> For LOC387715, two important studies have

shown that there is no statistical significant difference among the genotypes in response to PDT.<sup>(62,65)</sup> However, Sakurada et al. have recently shown that there is a pharmacogenetic association between the LOC387715 A69S variant and the long-term results after PDT in eyes with polypoidal choroidal vasculopathy (PCV). In this study, PDT was repeated every 3 months until the disappearance of angiographic signs of active lesions in 71 eyes of 71 patients with PCV who were followed-up for at least 12 months. There was a statistically significant difference in the visual acuity both at the 12-month and final visits ( $p = 0.002$  and  $P < 0.001$ , respectively) with the poorer acuity in patients with the higher T-allele frequency.<sup>(66)</sup> Immonen et al. have evaluated VEGF gene polymorphism and the outcome after PDT and showed a strong relationship between this gene and the treatment results. The VEGF gene polymorphic SNPs at rs699947 and rs2146323 were strong determinants of the anatomic outcome after PDT, but the SNPs studied were not associated with the presence of exudative AMD or with the CNV lesion size or configuration.<sup>(67)</sup> However, Tsuchihashi et al. did not show any association between VEGF rs 699947 SNP and the response to PDT.<sup>(68)</sup> Other genetic polymorphisms and its relationship with the response to PDT were evaluated but showed no statistically significant results.<sup>(62,67)</sup>

Recently, two studies have demonstrated the association between gene polymorphisms and the response to intravitreal injections of the anti-VEGF agents bevacizumab and ranibizumab.<sup>(69,70)</sup> Brantley et al. conducted a study in which eighty-six patients with exudative AMD undergoing treatment with 1.25 mg intravitreal bevacizumab in one eye were enrolled. Intravitreal injections were performed at 6-week intervals until there was no longer evidence of active neovascularization. Each patient was followed for a minimum of 6 months. The authors showed that post-bevacizumab VA was significantly worse in the CFH CC genotype than for the CFH TC or TT genotypes ( $p=0.016$ ). However, there was no significant difference in response to this drug according to the LOC387715 genotypes.<sup>(69)</sup> The other pharmacogenetic study published three years later was conducted to determine whether CFH genotypes had an effect on the treatment of exudative AMD with ranibizumab. A total of 178 patients were studied and, for each patient, an intravitreal injection of 0.5 mg of ranibizumab was performed at the initial presentation of an active choroidal neovascular complex. Subsequent injections were performed as needed and

patients were followed for a minimum of 9 months. In this retrospective study, Lee et al. found no difference in VA outcomes after ranibizumab treatment among the different CFH genotypes, in contrast to the previous study with bevacizumab. Nevertheless, over 9 months, patients with both risk alleles received approximately 1 more intravitreal injection.<sup>(70)</sup>

There is only one study with a large number of patients that addresses the preventive treatment of dry AMD related to the genetic polymorphisms. As we can observe, the majority of published articles about the therapeutic response of exudative AMD are related to the photodynamic therapy and many of them are controversial. Only two papers consider the intravitreal response to anti-VEGF agents according to the genetic polymorphisms. Since antiangiogenic therapy is now considered the gold standard treatment of exudative AMD, there is a long way to be traversed until treatment could be indicated according to the genetic profile of the patient. Additional studies with a larger number of patients, longer follow-up period and including more SNPs are important to establish a definite correlation between gene polymorphism and the therapeutic response in AMD. Only then may the treatment of this disease be recommended or modified based on genetic findings.

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