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Genetics of age-related macular degeneration: application to drug design

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Although age-related macular degeneration (AMD) is the leading cause of blindness in the elderly, treatment options are currently limited by a lack in the full understanding of disease pathogenesis. Much work has shown AMD pathogenesis to involve the complex interaction of genetic and environmental factors. While environmental factors such as smoking can directly result in a significant increase of risk, family and twin studies have long shown AMD to contain a significant genetic component and genome-wide studies have revealed an association between AMD susceptibility and polymorphisms in immune-related genes, most notably in *CFH* and *ARMS2/HTRA1* [1]. Technological advances have made genetic associations increasingly easy to identify; however, several key issues subsist in translating newly available genetic information into effective clinical therapy.

Unlike monogenic retinal diseases, AMD is a complex disorder that involves the interaction of multiple genetic loci and does not have a direct therapeutic target. In AMD, gene–gene interactions and their risk conferment are still unclear. Interaction between specific polymorphisms in *CFH* and *ARMS2/HTRA1* has been well demonstrated, but several studies report contradicting results. The lack of consistent conclusions in gene–gene interaction studies hints at complexity that needs further study before advancing to clinical application. Alongside the complex genetic factors involved in AMD are the gene–environment

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interactions whose contribution to disease is yet to be elucidated; that multiple environmental factors, such as obesity and smoking, in combination can compound genetic risk only further complicates the issue.

While gene therapy and stem cell therapy are promising fields for the treatment of ocular disorders, the current trend in AMD therapy is the use of VEGF inhibitors such as pegaptanib, ranibizumab and bevacizumab for the treatment of neovascular AMD [2]. The targeting of angiogenesis in neovascular AMD using VEGF inhibitors allows for clinical improvement despite the lack of a full understanding of pathophysiological events leading up to neovascularization. VEGF inhibitors have been shown to be a specific and effective regulator in neovascularization and are now a standard of care in the treatment of neovascular AMD. Variation in patient outcome however, has resulted in ongoing investigation of genetic influence on treatment response. To date, a study on the influence of single nucleotide polymorphisms in *CFH*, *ARMS2/HTRA1*, *VEGFA*, VEGF receptor *KDR* and angiogenesis genes *LPR5* and *FDZA* on patient response to ranibizumab is the most comprehensive analysis of association between known high-risk alleles and anti-VEGF treatment. The findings suggest that *CFH*, *ARMS2/HTRA1* and *VEGFA* high-risk alleles in combination are associated with poor response and additionally, that *CFH* and *ARMS2/HTRA1* genes have greater impact than *VEGFA* on ranibizumab treatment [3]. A very recent meta-analysis on *CFH* variants as well as a few recent studies on association between *CFH* and other AMD susceptibility genes with anti-VEGF response suggest emerging interest and potential in the field of AMD pharmacogenetics and the efforts being made toward personalized medicine [4,5].

Alongside persistence of poor responders and nonresponders, the clinical efficacy of VEGF inhibitors is challenged by the need for costly and indefinite intraocular injections that pose significant risk of complication. New research into RNA interference technology and gene therapy may serve to address these issues of pragmatism, as well as open up new targets for drug design. Initial testing of siRNA for the treatment of neovascular AMD suggested that anti-VEGF siRNA and, interestingly, even nonspecific siRNA may inhibit VEGF expression and subsequent neovascularization [6]. Further work has looked at targeting hypoxia-inducible factor genes such as *RTP801* that may result in downstream VEGF expression [7]. Lowering RTP801 expression results in inhibition of mTOR, a serine/threonine protein kinase that regulates cell growth, proliferation, motility and survival, leading to lower hypoxia-inducible factor and potentially suppressed VEGF expression, as well as reduction in endothelial cell response to VEGF [8]. The mechanism of action for RTP801 siRNA is independent of that of anti-VEGF and represents the open-ended potential of RNA interference technology to target not only angiogenesis but promote retinal neuron protection directly and, thus, produce better visual acuity outcomes than current anti-VEGF therapy.

Concurrently, recent US FDA approval of VEGF Trap-Eye™, a novel fusion protein of VEGF receptors that binds VEGF-A and VEGF-B isoforms with greater affinity than endogenous receptors, has added a viable treatment alternative to standard anti-VEGF therapy for neovascular AMD [9]. Clinical trials have shown that VEGF Trap-Eye produces noninferior results to anti-VEGF [10], with the advantage of fewer injections and thus

decreased risk of complication as well as a reduction in costs. While VEGF Trap-Eye may become part of the clinical treatment regimen for neovascular AMD, the soluble decoy receptor still faces many of the same issues of standard anti-VEGF and cannot yet be thought of as a solution for long-term treatment.

Advancements in the genetic pathogenesis of AMD, alongside improvements in safety and specificity, have contributed to discoveries made in gene therapy for AMD and may be the future of AMD treatment. Gene transfer using adeno-associated virus vectors or lentiviral vectors can produce long-term protein secretion in the retina as demonstrated by improvements seen in patients with advanced neovascular AMD treated with PEDF [11]. Gene transfer of soluble sFLT-1 has shown promise in several animal models [12,13].

Genetic discovery has not fueled the development of treatment options for geographic atrophy as it has for neovascular AMD. Currently, the front runner for treatment of geographic atrophy is rapamycin, originally an antifungal and immunosuppressant agent. The binding of rapamycin to its intracellular receptor results in mTOR inhibition and dysregulation of its signaling. The mTOR protein consists of two complexes, mTORC1 and mTORC2, of which mTORC1 is rapamycin sensitive and regulated by numerous factors, including several linked to AMD such as nutrient availability and hypoxia. Rapamycin is thought to suppress aging signals in RPE through mTORC1 inhibition, and RPE degeneration has been associated with increased activation of mTORC1 [14]. Treatment with rapamycin has been shown to prevent RPE degeneration and preserve photoreceptor function in response to oxidative stress [15]. These results in the mouse model suggest a basis for testing rapamycin, already in Phase II clinical trials for AMD, as a therapy for geographic atrophy [101].

Similar to interest in pharmacogenetic studies on gene variation and anti-VEGF response for neovascular AMD, analysis has been done on the association between *CFH* and *ARMS2/HTRA1* genotypes and antioxidant and zinc treatment in patients with advanced AMD, both geographic atrophy and neovascular AMD [16]. The study reported an association between specific *CFH* genotypes and supplementation with antioxidants and zinc, finding that patients with low-risk genotypes had greater reduction in AMD progression after treatment than those with high-risk genotypes. The authors speculate that benefits of supplements such as antioxidants and zinc are limited in patients with strong genetic predisposition.

Progress in gene discovery technology has expanded the field of AMD treatment research, making ventures into RNA interference and gene therapy possible and helping to establish significant parameters for clinical efficacy. The finding of gene association with current anti-VEGF therapy and growing evidence of treatment with siRNA operating through independent mechanisms point to future research into combination therapy for an increasingly targeted approach. While VEGF Trap-Eye and siRNA are in the near future, further investigation on the pathophysiology and genetics of AMD are needed for novel progress to be made in therapeutic options for AMD. The involvement of oxidative stress, inflammation, lipid metabolism, matrix protein, mitochondrial damage and apoptosis in AMD pathogenesis has been documented and studying these pathways could provide potential new targets for therapy. The role of inflammation in AMD has been confirmed

through numerous studies that indicate complement activation as well as macrophage infiltration [17]. A recent report of elevated serum C5a that stimulates production of IL-17 in T lymphocytes and increased serum IL-17 and IL-22 levels in AMD patients [18] points to novel therapeutic strategies for AMD on the horizon.

While novel discovery of AMD-related genes through genomic studies can help elucidate molecular mechanisms of AMD pathogenesis, and thus, aid in the future of drug design, we expect that the immediate and highly relevant need for an appropriate animal model will also play a significant role in the search for AMD therapies [19,20]. Expansion of genetic studies in AMD may also include investigation into noncoding RNAs such as intracellular microRNAs that may play a functional role in pathogenesis as well as extracellular microRNAs that may serve as biomarkers for disease. These important genes encode proteins that should be considered as therapeutic targets. Gene therapy, stem cell treatment and better ocular drug delivery will expand their applications for AMD [19]. Thus, we believe that the future of genetics research and drug design in AMD will emphasize further understanding of molecular mechanisms in AMD.

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Biography

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