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Age-related macular degeneration: genome-wide association studies to translation

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In recent years, genome-wide association studies (GWAS), which are able to analyze the contribution to disease of genetic variations that are common within a population, have attracted considerable investment. Despite identifying genetic variants for many conditions, they have been criticized for yielding data with minimal clinical utility. However, in this regard, age-related macular degeneration (AMD), the most common form of blindness in the Western world, is a striking exception. Through GWAS, common genetic variants at a number of loci have been discovered. Two loci in particular, including genes of the complement cascade on chromosome 1 and the ARMS2/HTRA1 genes on chromosome 10, have been shown to convey significantly increased susceptibility to developing AMD.

Unraveling the genetic basis of Mendelian disorders has been a success story of human genetic endeavor over the past three decades. Recent technological progress, in addition to the completion of the International HapMap Project in 2005 (ref. 1), has enabled greater elucidation of the genetic components of common polygenic diseases. The genome-wide association study (GWAS) has been the most common modality used in such investigations. GWAS attempt to identify single-nucleotide polymorphisms (SNPs) that occur more frequently within the genomes of sufferers of a disease than in a control population. It is generally accepted that these variations at single bases within the genome are proxies for a contributory variant, and their locations can therefore be used to infer genomic regions for disease association. In addition, because these associations are typically free from the confounding influences, such as social or behavioral factors, that can plague epidemiological research, they can be used in accordance with the principle of Mendelian randomization as surrogates for exposure when examining the effects of putative causal associations for disease. GWAS are most effective for common diseases whose causative alleles are derived from a common ancestor within the population and therefore follow the “common disease, common variant” hypothesis. This view—that disease-causing alleles are common within a population—was especially popular before the first GWAS.

Since the first GWAS in 2002, analyzing genetic susceptibility to myocardial infarction, more than 1,000 others of various sizes have been performed, testing a plethora of common diseases with differing degrees of success. Arguably, the best-known and most successful GWAS was by Klein et al. in 2005, a landmark study of the most common form of blindness in the Western world, age-related macular degeneration (AMD). This triggered numerous more detailed studies of AMD.

Since that time, GWAS have discovered a vast array of significant variants that have advanced our understanding of the biology of common disease. A striking example is Crohn’s disease: Duerr et al. and Rioux et al. implicated the interleukin-23 cytokine and autophagy pathways, respectively, in its pathology. Also, Sladek et al. showed a new role for β-cell zinc transport in type 2 diabetes, and multiple studies revealed new loci causing autoimmune disease. Nevertheless, GWAS have most frequently uncovered only variants with a small effect—that is, those of low penetrance with small odds ratios (a measure of the odds of a given allele being present in one population sample compared with those of its presence in another sample). In general, as a result, these studies tend to have little value in terms of predicting an individual’s risk. Furthermore, for many common conditions with familial components, such as schizophrenia, the majority of their heritability remains “hidden,” most likely in rare variants invisible to GWAS. Nonetheless promising. After providing brief overviews of AMD and common disease genetics, we outline the main recent advances in the understanding of AMD, particularly those made through GWAS. Finally, the true merit of these findings and their current and potential translational value is examined.

Key Words: age-related macular degeneration; complement cascade; genome-wide association studies; novel therapeutics

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GWAS and how it has improved our knowledge of the pathogenesis of AMD. Finally, the current and potential future clinical benefits derived from this, such as those granted by disease screening, are analyzed.

**AMD**

AMD is a progressive disease affecting the central portion of the retina: the macula. Early stages of the disease are characterized by an often asymptomatic accumulation of focal extracellular deposits, representing the classical AMD lesions, termed “drusen,” that form within Bruch’s membrane beneath the retinal pigment epithelium\(^1\) (Figure 1b). These drusen contain a barrage of different proteins, inflammatory mediators, and lipids,\(^1\) although, given the sheer number of candidates found in drusen it is difficult to identify what may act as a nucleating point of formation as opposed to being simply subsumed into the lesion over time. The severe, late-stage form of AMD affects 2.4% of individuals over the age of 50 in the United Kingdom,\(^1\) and with the population of the developed world aging, this prevalence is expected to increase. Late-stage AMD is subdivided into two types, so-called dry and wet forms (Figure 1d–f). Dry AMD is more common; well-demarcated “geographic” atrophy of the retinal pigment epithelium and underlying choroidal vessels causes progressive central visual loss. Wet, or neovascular, AMD is associated with severe visual loss and results from choroidal neovascularization breaking through Bruch’s membrane.

![Figure 1 Changes in ocular phenotype with age-related macular degeneration (AMD) progression.](image)

Retinal images acquired by fundoscopy show the varying stages of disease progression. (a) A schematic showing the location of the macular region of the eye where drusen formation leads to AMD. (b) A cross-sectional schematic demonstrating that drusen form within Bruch’s membrane, which itself is sandwiched between the retinal pigment epithelium (RPE) and the blood supply of the eye (choroid). (c) A healthy human eye, in which the radial blood vessels can be seen emanating from the optic disc (OD). The macula region is circled and is 5 mm in diameter. (d) In an eye presenting with early stages of AMD, drusen (white arrow) can be seen accumulating in the macula. (e) The presence of drusen may lead to choroidal neovascularization resulting in neovascular, or “wet,” AMD. (f) Geographic atrophy, or “dry” AMD, where there is complete loss of the RPE layer (seen here as the light yellow region in the macula).
Genetic contribution to AMD pathogenesis

FH is a key regulator of the alternative complement pathway, deactivating C3b that has been deposited both on host cells and, crucially, the extracellular matrix, such as the acellular Bruch's membrane. Deposited C3b otherwise activates a host immune response. FH is primarily synthesized in the liver but also is expressed locally in retinal pigment epithelium cells. This FH protein comprises 20 complement control protein (CCP) domains; the Y402H polymorphism is located in CCP domain 7. The exact causal effects of the many different CFH alleles are not yet fully understood. Indeed, since the original study of Y402H by Klein, other markers in weak linkage disequilibrium with Y402H have shown stronger associations with AMD, although these generally represent variants comparatively less common within the population. However, given that the CCP 7 region binds C-reactive protein and heparan sulfate (as methods of self-recognition), and that it is known that the Y402H polymorphism reduces FH binding to both C-reactive protein and heparan sulfate in Bruch's membrane, it is likely that this variant leads to a dysregulation of complement. Indeed, deposition of an increasing amount of the terminal membrane attack complex (which is indicative of increased complement turnover) under Bruch's membrane occurred in Y402H variant homozygous donor eyes compared with Y402Y “risk” donor eyes. Although unlikely to represent the initiating event of AMD, there is little doubt that a proinflammatory environment, driven by poor complement regulation conferred by the Y402H polymorphism, aggravates drusen formation and contributes to disease progression. A second major locus for susceptibility to AMD, at chromosome 10q26, was identified by a similar combination of targeted linkage studies and confirmatory GWAS. The mechanisms by which these effects are exerted are less well studied and are confounded by the presence of linkage disequilibrium between two genes, ARMS2 and HTRA1, that lie within a 200-kb region at the candidate locus. To date, the relative importance of each of these genes in AMD predisposition remains contentious. Nevertheless, it is tempting to note that, although the ARMS2 gene has not yet produced a detectable gene product in vivo, the Htra1 protein from HTRA1 is involved in extracellular matrix turnover, especially given the site of drusen formation—Bruch's membrane—forms part of the extracellular matrix.

FH and ARMS2/HTRA1 alleles represent the most influential of all the genetic factors contributing to AMD, and together they increase AMD predisposition by more than 40 times. Other genes, however—most of which also are involved in the complement pathway—have been implicated through GWAS and candidate studies of genes functionally related to complement. The genes encoding complement factor B and component 2 were tested using SNP association case–control studies,
which found these genes conveyed significant susceptibility\textsuperscript{39}; the same was seen for component 3.\textsuperscript{40} Later GWAS, using larger sample sizes, implicated other genes and pathways in AMD pathogenesis, in addition to confirming the contributions of suspected susceptibility genes. These include another complement gene, complement factor 1\textsuperscript{41}; genes associated with cholesterol and lipoprotein metabolism, APOE, LIPC, and CETP\textsuperscript{42}; extracellular matrix maintenance gene TIMP3; the atherosclerotic signaling FRK/COL10A1 variant\textsuperscript{43}; the angiogenesis gene VEGFA\textsuperscript{44}; and the TNFRSF10A/LOC389641 region.\textsuperscript{44} The AMD Gene Consortium recently found seven new disease loci: COL8A1-FILIP1L, IER3-DDR1, SLC16A8, TGFBR1, RAD51B, ADAMTS9, and B3GALT1.\textsuperscript{28} A summary of the most significant known genetic contributions to AMD and their proposed roles in its pathogenesis is included in Table 1.

In all, the 19 hitherto described loci conveying susceptibility to AMD are estimated to account for as much as 65% of its heritability.\textsuperscript{28} Even accounting for the significant proportion that remains unclear despite intense GWAS interrogation, this represents massive progress toward unraveling the genetic basis of the disorder, and it differs greatly from the extent to which we understand that of the majority of common diseases.\textsuperscript{45,46} We understand that of the majority of common diseases.\textsuperscript{45,46}

**HAVE GWAS FOR AMD BROUGHT ABOUT TRANSLATIONAL BENEFIT?**

It was forecast that GWAS success would convey considerable patient benefit; Wray et al.\textsuperscript{47} claimed that the “value of predictive SNPs could be reaped long before the causal mechanism of each contributing variant can be determined.” To assess this, we discuss the ways in which GWAS discoveries have altered our ability to predict AMD progression.\textsuperscript{47} We then analyze whether we are able to tailor individual therapies to each patient as a result,\textsuperscript{48} as well as describe the progress made toward developing novel therapeutics for AMD.

One aspect of GWAS that many expected to yield significant translational benefit was the use of putative genetic factors to predict and screen for disease (especially in individuals with a family history of the condition),\textsuperscript{49} with a view toward influencing choice of treatment or patient lifestyle. Indeed, a number of models have been designed for predicting the risk of an individual developing AMD\textsuperscript{50}; a recent one in particular claimed to be as much as 90% accurate.\textsuperscript{50} This represents remarkable progress and underlines the extent to which GWAS has advanced our knowledge of and ability to test for genetic factors for the condition. The advertised success of these models, especially relative to those for other common diseases, has coincided with the popular rise of commercial ventures such as 23andMe (https://www.23andme.com) and GenePlanet (http://www.geneplanet.com), which are able to assay genetic variants possessed by an individual. In theory, the ability to predict how, and roughly when, an individual will develop AMD would allow the clinician to personalize treatments based on genetic and environmental risk, thus providing the best tailored treatment. A major pitfall, however, is the current lack of interventions available to combat predicted onset of disease. This is exemplified by the National Health Service’s UK Genetic Testing Network not offering a test for AMD susceptibility (http://ukgttn.nhs.uk/find-a-test/). Furthermore, the recent warning given to 23andMe by the US Food and Drug Administration\textsuperscript{51} highlights the potential problems of such biomarker screening when no successful

### Table 1 Single-nucleotide polymorphisms associated with age-related macular degeneration and their affected genes

| DNA marker | Nearby genes | Joint P value in meta-analysis | Pathways/functions implicated |
|------------|--------------|-------------------------------|------------------------------|
| rs10490924/T | ARMS2/HTRA1 | 4 x 10\textsuperscript{-54} | Uncertain, possibly mitochondrial/cell growth |
| rs10737680/A | CH | 1 x 10\textsuperscript{-44} | Complement |
| rs429608/G | C2/CFB | 4 x 10\textsuperscript{-49} | Complement |
| rs2230199/C | C3 | 1 x 10\textsuperscript{-41} | Complement |
| rs5749482/G | TIMP3 | 2 x 10\textsuperscript{-26} | Extracellular matrix degradation |
| rs4420638/A | APOE | 2 x 10\textsuperscript{-20} | Lipoprotein metabolism, atherosclerosis |
| rs1864163/G | CETP | 7 x 10\textsuperscript{-16} | Lipoprotein metabolism, atherosclerosis |
| rs943080/T | VEGFA | 9 x 10\textsuperscript{-16} | Angiogenesis |
| rs13278062/T | TNFRSF10A | 3 x 10\textsuperscript{-15} | Cell death |
| rs13081855/T | COL8A1-FILIP1L | 4 x 10\textsuperscript{-13} | Extracellular matrix/angiogenic activity of endothelial cells |
| rs8017304/A | RAD51B | 9 x 10\textsuperscript{-11} | Homologous recombination |
| rs4698775/G | CFI | 7 x 10\textsuperscript{-11} | Complement |
| rs920915/C | LIPC | 3 x 10\textsuperscript{-11} | Lipoprotein metabolism, atherosclerosis |
| rs334353/T | TGFBR1 | 3 x 10\textsuperscript{-11} | Widespread, including angiogenesis |
| rs8135665/T | SLC16A8 | 2 x 10\textsuperscript{-11} | Lactate transport |
| rs3130783/A | IER3-DDR1 | 2 x 10\textsuperscript{-11} | Cell death/growth |
| rs6795735/T | ADAMTS9/MIR548A2 | 5 x 10\textsuperscript{-9} | Proteoglycan cleavage, inhibition of angiogenesis |
| rs3812111/T | COL10A1 | 2 x 10\textsuperscript{-9} | Atherosclerosis |
| rs9542236/C | B3GALT1 | 2 x 10\textsuperscript{-9} | Glucose transport |
intervention exists to modify disease progression. The clinical impact of screening in the case of AMD hinges on the development of viable therapeutics to influence disease progression or the ability of clinicians to recommend effective lifestyle changes to modulate risk.

The substantial contribution of environmental factors to AMD raises the possibility of altering patient lifestyle in response to genetic testing. Smoking, for example, is a well-established risk factor for the condition and, theoretically, a knowledge of genetic risk might encourage an individual to cease doing so. However, whether an increased risk of developing a chronic disease, when smoking is known to predispose to many other such diseases, would actually influence the lifestyle of a given individual is debatable. For example, Hollands et al. showed that patients with a familial risk for Crohn’s disease, additionally predisposed by smoking, were no more likely to stop the habit than those without. Also, the dietary intake of a number of substances, notably those with antioxidant properties such as the carotenoids β-carotene, lutein, and zeaxanthin and vitamins C and E, is known to affect progression to advanced AMD. However, studies attempting to prove that modifying dietary intake of such substances is significantly preventive of AMD have so far been inconclusive.34,55

The greatest advancement in the clinical approach to AMD has been the introduction of antiangiogenic therapies for wet AMD56,57; the most widely used is the vascular endothelial growth factor–inhibiting monoclonal antibodies bevacizumab and ranibizumab.58 Wet AMD, the less common form of the disease, affects vision more severely, and, although great benefit has been derived from this therapy, it only halts disease progression and does not prevent onset, nor does it reverse damage already caused to the vision. Furthermore, it is important to note that the implementation of antiangiogenic agents as a method of treating AMD was brought about independent of GWAS. In fact, despite the different pathways recently implicated in AMD pathogenesis, novel interventions that successfully exploit this knowledge remain elusive, and dry AMD remains untreatable.

However, GWAS have identified the importance of complement activation via its alternative pathway (the pathway controlled by FH) in AMD pathogenesis. As such, a number of complement-based therapeutics are currently undergoing clinical trials (see Table 2) or are currently in preclinical development. Eculizumab, an antibody against the complement protein C5, was the first logical choice because it was already in clinical use for other complement-mediated disease (e.g., atypical hemolytic uremic syndrome). The use of eculizumab for treating dry AMD, however, failed to affect the progression of geographic atrophy. This is perhaps unsurprising because this drug targeted the complement pathway at a point downstream of the alternative activation pathway: All GWAS-identified SNPs are in genes whose proteins are involved in an alternative pathway, not the lectin, classical, or terminal pathways.60 Similarly, other therapeutics that also target C5—as either an antibody (LFG316; Novartis) or an aptamer-based C5 inhibitor (Zimura; Ophthotech)—are currently in ongoing clinical trials.

A slightly different approach is represented by the drug lampalizumab (Genentec/Roche), an antibody Fab fragment raised against complement factor D. This has great promise, targeting only the alternative activation pathways of complement (the one associated with AMD) and leaving the remaining pathways unaffected, thus providing patients with continued protection against bacterial infections. Phase II trials have been completed, delivering lampalizumab by intravitreal injection for geographic atrophy. While the results remain unpublished, Roche has indicated that efficacy has been seen and a phase III trial is commencing.

Other putative therapies also are under consideration. These include antibodies against properdin and complement factor B, both of which are essential for the activation of complement via the alternative pathway, and even the introduction of specifically designed “mini” complement regulators in an attempt to readress the imbalance of complement activation in the back of the eye. Given the early stages of such research, assessing how it will translate into the clinic remains difficult, but nonetheless it demonstrates the considerable effort being put into complement-mediated therapeutics for AMD.

### Table 2 Current complement-based therapeutics directed against age-related macular degeneration (AMD)

| Therapeutic (alternate name)* | Treatment type | Complement target | Company         | Targeted AMD form | Clinical trials |
|------------------------------|----------------|-------------------|------------------|-------------------|-----------------|
| POT-4                        | Protease inhibitor | C3                | Potentia        | Wet               | NCT00473928; phase I |
| Eculizumab                  | Monoclonal antibody | C5                | Alexion         | Dry               | NCT00935883; phase II |
| LFG316                      | Monoclonal antibody | C5                | Novartis        | Dry               | NCT01527500; phase II |
| Zimura (ARC1905)            | Aptamer-based inhibitor | C5                | Ophthotech      | Dry               | NCT01535950; phase II |
| Lampalizumab                | Antibody Fab fragment | Factor D           | Genentech/ Roche | Dry               | NCT02247479; phase III |

*aIn some instances, therapeutics have previously been known by a different name. bEculizumab was originally a treatment for other complement-mediated diseases and was in clinical use before genome-wide association studies’ association of complement with AMD.*

### Powerful Genetic Research to Uncover Missing Heritability

As previously mentioned, ~35% of the heritability of AMD remains undiscovered. Indeed, the inability of GWAS to elucidate the entire genetic component of common diseases is a recurring theme; for some conditions, the vast majority of their heritability...
remains unknown. This failure of GWAS to consistently find individually significant genetic risk factors has led to the rise in popularity of a view of common disease genetics opposing the "common disease, common variant" theory. This new viewpoint is known as the "common disease, rare variant" (CDRV) hypothesis, originally put forward before the first GWAS. CDRV states that genetic factors causing common disease can be rare within a population, and were they to contribute more to the heritability of such conditions, it would correspond to the selective pressures upon such variants within the gene pool. In other words, there exist variants of great significance that are too rare for GWAS to uncover. The degree to which these two hypotheses prevail seems to differ from one common condition to the next.

It is thought that elucidation of the hitherto unknown genetic component of AMD, possibly caused by rare variants overlooked by GWAS, would help to elucidate the underlying pathogenesis, fueling drug discovery. These variants could be in the form of new loci, exposing novel pathways as important to pathogenesis, or new variants within known loci, helping to elucidate exactly the functional consequences of mutations. Here, the next-generation sequencing era introduces exciting new possibilities; singling out genetic variants in individuals, no matter how rare within a population, will provide a greater range of genetic factors from which to study gene function and disease mechanisms. The potential impact of this type of study for AMD was illustrated by Raychaudhuri et al. In that study, high-throughput analysis identified a high-penetration haplotype for AMD, a rare CFH variant, and its functional consequences were examined. The potential advantages conveyed to AMD genetics, and indeed common disease genetics, by the accurate and rapid sequencing of human genomes are therefore significant.

Furthermore, targeted therapeutic approaches will require full comprehension of the biology of a condition: The new wave of potential therapies for AMD, such as novel attempts to disrupt the angiogenesis pathway, complement inhibitors, and integrin inhibitors, has resulted from the success of studies involving functional analysis of molecules and pathways. An example is the study of the functional consequences of the common Y402H FH polymorphism and the fact that it alters the ability of FH to regulate complement at the site of disease pathogenesis. Functional studies of this ilk are anticipated to help discover future potential treatments for AMD, and greater knowledge of the "hidden" heritability of AMD will help their success.

CONCLUSIONS

The GWAS for AMD are a much-celebrated scientific advancement. Although these have provided significant insight into the genetic component of the condition, it has been shown here that the translational benefit derived to date, beyond predictive disease susceptibility, has been limited. It goes without saying, though, that in an ever-changing field with much ongoing research, it is fair to expect greater elucidation of the hidden heritability of the condition (especially by next-generation sequencing) and subsequently more effective functional analysis of the mechanisms underlying AMD pathogenesis in the near future. It is hoped that these advancements will facilitate the discovery of novel effective treatments that will revolutionize clinical management of AMD and simultaneously improve the value of predictive genetic screening.

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DISCLOSURE

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