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New era for personalized medicine: the diagnosis and management of age-related macular degeneration

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Abstract

It can be argued that age-related macular degeneration is one of the best characterized complex trait diseases. Extensive information related to genetic and environmental risk factors exists, and a number of different biological pathways are strongly implicated in its aetiology. Along with recent improvements in high throughput and relatively inexpensive genetic technologies, we are now in a position to consider developing a presymptomatic, personalized approach towards the assessment, management and treatment of this disease. We explore the applicability and challenges of this approach if it is to become commonplace for guiding treatment decisions for individuals with pre-existing disease or for those at high risk of developing it.

Keywords

age-related macular degeneration; genetic; risk factor

Background

Age-related macular degeneration (AMD) is the leading cause of irreversible loss of vision among elderly populations in the developed world.^{1,2} Clinically, the late, or advanced, stages of AMD – classified as geographical atrophy and choroidal neovascularization – are associated with the most significant visual impairment in affected individuals, although individuals with early-stage disease can also experience significant visual symptoms. Advances in the treatment of the neovascular complications of AMD have emerged recently, but there is still little to offer the majority of people with geographical atrophy or earlier forms of the disease in the way of treatment.

Australian socioeconomic data indicates that the disease currently costs Australia \$2.6 billion per annum, and the continued trend for increased life expectancy predicts there to be a doubling in the number of people with AMD with costs reaching \$59 billion³ over the next

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20 years. Thus, there is a real need to better diagnose AMD, its age of onset and rate of progression, to understand and modulate pathways and ‘environmental’ elements that determine and drive it and to develop additional treatment strategies or delay its progression.

AMD as a complex disease

Non-genetic risk factors

Age-related macular degeneration is a complex trait genetic disease modulated by various non-genetic, or ‘environmental’ risk factors. A number of risk factors have been reported to influence AMD, including non-modifiable risk factors such as age, gender and family history as well as infectious agents.^{4–6} Modifiable risk factors, such as smoking, diet, higher body mass index, serum cholesterol levels, cataract surgery, cardiovascular disease, hypertension and sunlight exposure have also been implicated.⁵ Of the modifiable risk factors, smoking has been shown consistently to be associated with disease, with an approximate twofold increased risk of disease in smokers⁷ and elevated body mass index also appears to be mostly associated with early or AMD progression with a similar twofold increased risk of disease.⁸ Observations related to other risk factors other than smoking have not been replicated and/or have been inconsistent in their associations. These inconsistencies may be a result of several factors, but one important source of variability likely relates to the lack of consideration given to each individual’s underlying genetic susceptibility.

Genetic associations

Major genetic advances have been made over the past few years in the identification of risk and protective genetic variants associated with AMD. Several genes have now been identified as having strong and significant associations with AMD (Table 1). These genes account for a substantial proportion of the genetic predisposition associated with the disease.^{10,12,19,21} Of the genes thus far identified, a majority play roles in the immune/inflammatory system. These include the complement factor H gene (*CFH*) on the long arm of chromosome 1,^{12–15} the complement factor B (*CFB*) and the complement component 2 (*C2*) genes localized within the major histocompatibility complex class III region on chromosome 6,¹⁰ the complement *C3* gene on chromosome 19p¹¹ and the *CFH* paralogous genes (*CFHR3*, *CFHR1*, *CFHR4*, *CFHR2* and *CFHR5*) that are arranged in tandem on chromosome 1 and present as partial duplications of the *CFH* gene associated with a protective effect for AMD.¹⁶ Additionally, two additional loci contain AMD-associated genes that do not have as obvious a role in immunity. These include a locus within the vicinity of the hypothetical *ARMS2/LOC387715*^{17,18} and HtrA serine peptidase 1 (*HTRA1* also known as *PRSS11*) genes^{19,20} on chromosome 10q and the apolipoprotein E (*APOE*) gene on chromosome 19.⁹ Associations with a number of additional genes – including the *ABCA4*,²² *FIBLN6* (Hemicentin),²³ *TLR3*²⁴ and *SERPINC1* genes²⁵ (Table 2) have been suggested, but in most cases these have not been verified/replicated in subsequent studies. Readers with more interest in these genes should refer to reviews in this area.^{39,40}

Single nucleotide polymorphisms (SNPs) and disease

A number of genetic variants or SNPs have been identified within AMD-associated genes. One of the most highly investigated SNPs to date is rs1061170 at nucleotide position 1277

within exon 9 of the *CFH* gene (MIM 134370). The T-to-C change at this SNP results in an amino acid change from a tyrosine at position 402 to that of a histidine (Y402H).^{12–15} The C nucleotide variant at this site has been reported as a risk susceptibility allele for AMD in many western and some Asian populations with the majority of these studies, indicating a significantly increased risk of approximately twofold in the heterozygous (CT) state increasing up to a 10-fold risk in the homozygous (CC) state.⁴¹ In addition, the CC genotype also appears associated with a significantly earlier age (approximately 7 years) of exudative disease onset, indicating a multifactorial role for this SNP in disease susceptibility.⁴¹

Multiple SNPs and risk of AMD

It is entirely possible that more than one allelic variant within a disease-associated gene may collectively contribute to disease susceptibility. In the case of the *CFH* gene, for example, several SNPs have been shown to be strongly associated with AMD, including several that are more highly associated with increased risk of AMD than the Y402H variant. It was observed in one of the initial *CFH* studies that the synonymous A473A variant in exon 10 (odds ratio [OR] = 3.42, 95% confidence interval [CI] [2.27–5.15]) and rs203674 in IVS10 (OR = 2.44, 95% CI 1.97–3.03) exhibit more significant associations with AMD.¹⁵ Subsequently, as many as 20 additional SNPs in the *CFH* gene have been reported as being more strongly associated with AMD than the Y402H variant.^{42,43} In addition, none of these variants appear to alter the *CFH* protein, leading to speculation that they may regulate *CFH* gene expression or that of nearby complement genes.⁴³

When considering multiple genetic associations with diseases, either through multiple SNPs within a gene, or different SNPs in different genes, as for instance with the *CFH* gene and the *C2/BF* and *C3* genes, disease-associated SNPs can be grouped into strings of SNPs – commonly referred to as haplotypes – to better define their association with the risk for developing, or protection against developing disease.^{10,15,16} In the case of the *CFH* gene, one of the initial studies identified a series of disease-associated SNPs (including Y402H), where eight SNPs defined five *CFH* haplotypes with >5% frequency (Table 3).¹⁵ The two most common haplotypes represent 85% of all haplotypes found in two large White cohorts; the most prevalent haplotype is strongly associated with AMD risk and the next most prevalent with strong protection against development of the condition. Several studies have now confirmed the association of these *CFH* haplotypes in different populations.^{44,45}

Genetic risk factors and AMD progression

The majority of AMD genetic association studies conducted thus far have assessed the genetic risk associated with late-stage disease. A few recent studies have examined the role of these genes in modifying the risk and rate of disease progression. One recent study, for example, has documented a significantly increased risk of progression of AMD in the female population with the $\epsilon 2$ genotype relative to the $\epsilon 4$ genotype of the *APOE* gene (OR 4.8, 95% CI 1.19–19.09), suggesting a potential gender involvement in disease risk.⁴⁶ Several studies have now also demonstrated that the Y402H of the *CFH* gene shows significant association with increased AMD progression (OR 2.43, 95% CI 1.07–5.49),^{19,47,48} indicating a role for this gene in both progression as well as in late-stage disease.

Common *versus* rare gene variants in AMD

The ability to screen large numbers of SNPs has been instrumental in driving gene discovery in AMD. Most of the current commercial SNP arrays used for genome-wide association studies have been designed with excellent coverage of common SNPs, but with limited potential to capture rare and low-frequency variants (i.e. those with a minor allele frequency below 5%).⁴⁹ Although these common variants explain a substantial proportion of disease risk in the population it is still unclear as to what proportion of AMD, or what differences in phenotypic presentation is explained by SNPs with a low minor allele frequency of intermediate penetrance. The current lack of identified rare variants, however, does not necessarily imply that they do not play a role in AMD. Such variants, if identified, may in fact play a pivotal role in the disease process, thus collectively explaining a greater proportion of familial risk and providing improved prediction of disease risk compared with common variants.^{50,51} The role of re-sequencing of selected associated gene regions in large numbers of individuals in different populations or whole genome sequencing such as in the thousand genome project⁵² may be pivotal in helping to identify rare variants that may impact susceptibility to AMD.

Gene–gene and gene–environment effects in AMD

In complex genetic diseases such as AMD, the ability to predict risk will be greatly improved if the effects derived from genetic variants are also considered collectively, and in combination with other, non-additive factors, often described as gene–gene or gene–environment interactions. Interestingly, minimal gene–gene interaction (epistasis) has thus far been observed between the different AMD-associated genes, suggesting that they might be independent and non-interactive.^{20,53,54} Alternatively, it may be that the studies conducted to date may be underpowered to allow detection of such effects. Thus, larger study populations will likely be required to identify such interactions.

In the case of gene–environment interactions, a number of risk factors have been examined with varying results of interaction. For instance, in one study, individuals with the CC risk genotype of Y402H of the *CFH* gene had a significantly increased risk of progression of disease (OR 2.43, 95% CI 1.07– 5.49).⁴⁸ Likewise individuals in the upper tertile of antibody titre to the bacterial pathogen *Chlamydia pneumoniae* were associated with an increased risk of disease progression (OR 2.6, 95% CI 1.24–5.41), as compared with those in the lowest tertile.⁵⁵ However, when individuals had both the CC risk genotype at the *CFH* Y402H variant and the highest tertile of bacterial pathogen *C. pneumoniae* it resulted in a combined risk of OR 11.8, 95% CI 2.1–65.8⁴⁸ that was substantially higher than that of the individual factors on their own. Furthermore, biological interaction studies provided through the use of risk ratios also support the notion that exposure to both of these factors is multiplicative rather than additive in nature.⁴⁸

However, not all environmental factors act in this multiplicative manner. In the case of smoking, we identified a twofold increased risk with progression of AMD, but there was no apparent multiplicative effect when *CFH* genotype was also considered.⁴⁸

Prospects for personalized medicine in AMD

One of the key promises of the genomic revolution is the hope that we will one day be able to provide individuals and health-care providers with sufficient diagnostic information related to AMD risk that one can better undertake decision-making, personalize treatment and motivate lifestyle improvements with improved outcomes and more prudent use of the health-care dollar. Indeed, personalized medicine already exists for monogenetic disorders such as Huntington disease, phenylketonuria (PKU) and hereditary forms of cancer. Yet, for complex diseases such as AMD it represents a major challenge.

In the field of AMD, one important goal will be to develop a predictive test that can discriminate between those individuals who will develop severe vision-threatening disease and those who will not; another to characterize the rate of disease progression and conversion to late-stage disease; and yet another to define one's likely response to treatment modalities. In the latter case, some small studies have already indicated that that an individual's genotype can influence outcome following treatment whereby individuals with the 'CC' homozygous risk genotype of Y402H of the *CFH* gene showed greater loss of visual acuity following treatment with intravitreal bevacizumab.⁵⁶ Whereas individuals with a CC risk genotype and undergoing ranibizumab treatment had a 37% statistically significant higher risk of requiring further intravitreal injections compared with those individuals with the TT or TC genotype ($P = 0.04$).⁵⁷

It will be important to include as many informative, AMD-associated variants as possible when designing diagnostic platforms. Reliance on a limited number of variants will clearly be misleading. As an example, the homozygous *CFHY402H* CC genotype is present in approximately 38.6% of cases, but also in approximately 9.7% of individuals without AMD.⁴¹ Although there is a substantially increased prevalence of the homozygous risk Y402H *CFH* genotype in cases as compared with controls, approximately 10% of the age-matched population who carry this genotype had not developed AMD. Thus, prediction of AMD susceptibility based on this single SNP alone would not be highly specific. Genetic testing based on the presence of this C risk allele alone would find that approximately 46% of cases and 55% of controls⁴¹ were heterozygous for the CT genotype. Consequently, risk of disease may differ only marginally between carriers and non-carriers of particular risk variants of one single susceptibility gene.

Racial background also impacts on risk as it is known that the C risk allele of *CFHY402H* shows ethnic variability in that the strong association with AMD in populations of mainly European descent is not observed in Japanese,^{46,58} Korean⁵⁹ or Chinese individuals.⁶⁰ This most likely reflects the low frequency of this variant in these populations.

Assigning estimates of disease risk for AMD will be even more powerful if both gene–gene (epistasis) and gene–environment interactions are included in the assessment. The importance of these interactions will differ between individuals and depend upon the stage of the disease at the time the diagnostic assessment is made. It has been clearly documented that AMD results from the joint effects of multiple genes and non-genetic modulators. Thus, the use of presymptomatic diagnostic testing – or genetic profiling – should include the assessment of all informative genetic variants in multiple disease-associated genes,

alongside information relating to documented, disease-associated ‘environmental’ factors that collectively act together to shape an individual’s susceptibility to AMD.

Predictive power of genetic testing of multiple SNPs

It is estimated that greater than 50% of AMD individuals present with high-risk alleles at the *CFH*, *LOC387715* and *C2/BF* loci.^{10,12,19,21} In particular, analysis of five SNPs in these genes indicated that 10% of the study population had a 40-fold increased risk of AMD, whereas individuals who were homozygous for all risk variants had a 285-fold greater risk compared with the lowest risk group.⁵³ However, although this comparison is valid it also argues as to whether these findings improve prediction of end-stage AMD in individuals at risk.⁶¹ Comparison of extreme tails of the genotype spectrum (high-risk homozygous individuals vs. low-risk homozygous individuals) may indeed result in the ability to estimate very large risks, but such comparisons may be totally different to those obtained from the general population. In a study by Despriet *et al.* (2007),⁶² it was shown that when a reference group was chosen based on the average risk in a population and compared with those with a high-risk genotype at these three loci, the risk of AMD was 14-fold higher compared with the population risk whereas individuals who carried only low-risk genotypes had a 20-fold decreased risk.⁶² Although both the estimates of odds ratio of 285⁵³ and odds ratio of 14⁶² indicate a considerable deviation from the general population risk, the latter interpretation of the data perhaps provides a more closely aligned AMD risk estimate relevant for clinical practice.

In some ways, all of the above-mentioned considerations are exacerbated when we consider the fact that there are multiple genetic variants in multiple genes implicated in AMD (as compared with single DNA variants in monogenic diseases), and that ‘environmental’ risk factors will vary from person to person and from population to population. These risks may vary with stage of disease, for example, factors contributing to early disease may differ to those that lead to progression, or to late-stage disease or to response to treatment. Moreover, the effects may be different as they relate to various phenotypes of AMD. Clearly, the testing of multiple susceptibility variants alone is unlikely to yield a reliable prediction model for AMD, but the question remains as to what extent inclusion of additional genetic variants will have on improving this disease prediction. Including the role of multiple environmental factors in any model will also be required if we are to improve risk profiles for individuals.

On the other hand, it is extremely fortunate that our knowledge of both the genetic and non-genetic risk factors associated with AMD is immense. AMD is clearly the most-well-characterized of the complex trait diseases to date. Along with our profound knowledge of the disease comes an opportunity to develop an AMD diagnostic platform that is not only predictive in nature, but also highly sensitive and specific. Indeed, our ability to predict advanced AMD using a combination of SNPs in the *CFH*, *CFB/C2*, *ARMS2/HTRA1* and *C3* genes is high.⁵³ One study suggests that the predictive value of genetic testing to discriminate those individuals that will develop late-stage AMD has recently been modelled at 80%.⁶²

There are many issues to be resolved during the development of a sensitive and specific AMD-based diagnostic platform. Nonetheless, several direct to consumer companies

currently offer high-density SNP arrays or genome sequencing with the aim of providing customized genetic profiles for AMD. One issue is how useful these tests are to the individual and whether screening offers improved clinical outcome. The current review is not intended to interrogate the ethical, legal or scientific merits of such testing but to highlight that such tests already exist and that much has already been written on the subject and the reader is encouraged to read a number of reviews on these issues.^{63–65} In addition, the reader is also encouraged to view an article on the potential pros and cons of diagnostic testing in an ophthalmology setting.⁶⁶

We are already aware that a number of genes are involved in AMD indicating that an individual's genetic make-up is likely to have a profound influence on the way that we think of personalized treatment options for this disease. For instance knowledge pertaining to a predetermined, genetic-based response to anti-VEGF treatment could potentially dictate the nature of therapy received and the progression and course of neovascular AMD. Protective haplotypes may also be found which may be efficacious during treatment of late-stage, exudative disease. Given the large number of people with neovascular AMD, currently and in the future who are likely to require anti VEGF treatment, understanding of the potential pharmacogenetic relationship is needed to best guide the use and maximize the benefits of these expensive and highly effective interventions.

New treatments in preclinical development such as complement replacement currently being developed by the company Optherion will allow augmentation of faulty genes in the complement pathway. However, this approach will be most applicable to those individuals who have known AMD risk variants. In addition, different genetic haplotypes in individuals may require modifications in such treatment to achieve the most beneficial result depending on the stage of the disease.

Conclusions

Our knowledge of the genetic and non-genetic 'environmental' risk factors involved in AMD makes it one of the best characterized complex trait diseases. Indeed, AMD may lend itself to the forefront of personalized management and intervention, long before that of other common complex genetic diseases such as diabetes and cardiovascular disease. Clearly, a wealth of new information will soon be made available to clinicians to help them better diagnose and manage their patients at risk or with AMD. Systems will clearly need to be established to educate clinicians as to what the information they receive from screening labs actually means for management of the patient. Similarly, counselling services will need to be made available to help patients to interpret their risk profiles. These requirements, which will be necessary to take full advantage of this new medical revolution, currently lag behind the rapid advances made in the acquisition of this knowledge; however, it can be anticipated that once prediction and/or progression tests are in place or available internationally, it will be individuals at high risk of disease who will drive the revolution to use this information.

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Table 1

Genes identified as associated with AMD and verified in subsequent studies

Gene symbol	Immune related	Chromosome position	Year first associated with AMD
ApoE	Yes	19q13	1998 ⁹
BF/C2	Yes	6p21	2006 ¹⁰
C3	Yes	19p13	2007 ¹¹
CFH	Yes	1q32	2005 ^{12–15}
CFHR 1–5	Yes	1q32	2006 ¹⁶
LOC387715/HTRA1	NA	10q26	2005/6 ^{17–20}

AMD, age-related macular degeneration; *CFH*, factor H gene.

Table 2

Genes initially identified as associated with AMD but not verified in subsequent studies

Gene	Immune related	Chromosome location	Year identified
ABCA4	NA	1p22	1997 ²²
ACE	NA	17q23	2002 ²⁶
CFI	Yes	4q25	2009 ²⁷
CST3	NA	20p11	2002 ²⁸
CX3CR1	Yes	3p21	2004 ²⁹
ERCC6	NA	10q11	2006 ³⁰
Fibulin 5	NA	14q31	2004 ³¹
Fibulin 6 (hemicentin)	NA	1q25	2003 ²³
HLA	Yes	6q	2005 ³²
LRP6	NA	12p11	2006 ³³
PEDF	NA	17p13	2008 ³⁴
PON1	NA	7q21	2001 ³⁵
SERPING1	Yes	11q12	2008 ²⁵
SOD2	NA	6q25	2005 ³⁶
TLR3	Yes	4q35	2008 ²⁴
TLR4	Yes	9q32	2005 ³⁷
VEGF	NA	6p12	2006 ³⁸
VLDLR	NA	9p24	2006 ³³

AMD, age-related macular degeneration; *CFH*, factor H gene.

Table 3

Significantly associated *CFH* risk and protective haplotypes

Haplotype	Risk/protective	SNP variant								Odds ratio heterozygous/ homozygous
		1	2	3	4	5	6	7	8	
H1	Risk	C	C	G	T	C	T	A	G	2.46/3.51
H2	Protective	C	T	A	T	T	G	A	G	0.54/0.27
H3	Neutral	T	C	G	T	T	G	G	T	NS
H4	Protective	C	C	G	C	T	G	A	G	0.48
H5	Neutral	T	C	G	T	T	G	A	G	NS

SNP variant: 1 = rs3753394 (−257), promoter 2 = rs529825 (IVS1), 3 = rs800292 (I62V), 4 = rs3766404 (IVS6), 5 = rs1061170 (Y402H), 6 = rs203674 (IVS10), 7 = rs3753396 (Q672Q), 8 = rs1065489 (D936E). *CFH*, factor H gene; NS, non significant; SNP, single nucleotide polymorphism.