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Genetic susceptibility to age-related macular degeneration: a paradigm for dissecting complex disease traits

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Age-related macular degeneration (AMD) is a progressive neurodegenerative disease, which affects quality of life for millions of elderly individuals worldwide. AMD is associated with a diverse spectrum of clinical phenotypes, all of which include the death of photoreceptors in the central part of the human retina (called the macula). Tremendous progress has been made in identifying genetic susceptibility variants for AMD. Variants at chromosome 1q32 (in the region of *CFH*) and 10q26 (*LOC387715/ARMS2*) account for a large part of the genetic risk to AMD and have been validated in numerous studies. In addition, susceptibility variants at other loci, several as yet unidentified, make substantial cumulative contribution to genetic risk for AMD; among these, multiple studies support the role of variants in *APOE* and *C2/BF* genes. Genome-wide association and re-sequencing projects, together with gene-environment interaction studies, are expected to further define the causal relationships that connect genetic variants to AMD pathogenesis and should assist in better design of prevention and intervention.

INTRODUCTION

A vast majority of common diseases are complex and multi-factorial, resulting from the interplay of genetic components and environmental factors. As no single gene or genetic variant can on its own cause the disease pathology, complexities associated with common diseases present unique challenges for management and therapy. While genetic defects have been identified for over 2000 Mendelian diseases (generally rare and affecting small population subsets) during the last two decades (Online Mendalian Inheritance in Man, http://www.ncbi.nlm.nih.gov/sites/entrez?db = OMIM), the progress towards understanding more frequent multi-factorial diseases has been painfully slow until recently. Completion of the human genome sequence and cataloging of millions of common single nucleotide polymorphisms (SNPs) (1–3) have led to rapid and unprecedented advances in uncovering genetic contributions of disease susceptibility for several complex diseases, including diabetes, coronary artery disease and macular degeneration (4–9).

Age-related macular degeneration (AMD) is an ideal prototype of a complex and common disease trait, and genetic studies of AMD illustrate both the promise and challenges of new gene-mapping approaches. Early-onset maculopathies, such as Stargardt's disease, have long been known to have hereditary basis. In contrast, by mid-1990s, only a handful of publications suggested role of genes in determining AMD risk (10–12), and it was difficult to convince most clinicians and scientists about the value of genetic studies. Recent investigations have not only unambiguously established the role of genetic variants in AMD pathogenesis, but have also made it feasible to uncover the role of gene–gene and gene–environment interactions for this debilitating blinding disease. In this review, we will summarize the progress in unraveling the genetic basis of AMD and present directions for future studies that can be applicable to other multi-factorial disorders.

PREVALENCE, RISK FACTORS AND CLINICAL PHENOTYPES

AMD can be defined as aging-associated progressive degeneration of photoreceptors and/or retinal pigment epithelium (RPE) in the central part of the human retina (called the macula),

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eventually leading to the loss of central vision. It is the major cause of uncorrectable visual impairment in the elderly population of the developed countries (13–15). AMD affects over 1.7 million people in US alone, and this number is expected to reach three million by the year 2020 (13). With increased life expectancy, this devastating disease will continue to have a significant public health impact on the quality of life worldwide (16,17).

Clinical presentation of AMD is rather diverse (Fig. 1). Small and hard macular drusen occur as part of the normal aging process and do not necessarily predict the disease (18). Early stages of AMD include atrophy of the RPE (18). Large and soft drusen in the macula are identified as strong risk factors for the development of advanced forms of AMD, which include central geographic atrophy (GA) and choroidal neovascularization (CNV) (19). Advanced age and family history are the two major risk factors (20). However, a number of environmental factors can also contribute to clinical manifestations of AMD; these include smoking, vascular disease, UV exposure and nutritional status (15,20).

For genetic studies, a clear definition of the disease status and/or phenotype is an essential aspect of the study design. The phenotypic determination of affected status of controls is equally important to the success of genetic studies. Since AMD is a widespread late-onset disease, the most effective controls are older than the typical age of onset for the disease (21). No consensus has emerged on an optimal disease classification and grading scheme. Instead, several grading systems are currently being used in different population-based and cohort-based studies (22–25). As susceptibility to distinct AMD subtypes appears to be driven by different genetic risk factors, we expect that attention to disease classification will be an important aspect of future genetic studies of AMD. In particular, we expect it will help to elucidate the molecular switches that ultimately result in distinct phenotypes for different individuals.

Population-based studies have revealed significant differences in the incidence and prevalence of AMD subtypes among different ethnic/racial groups in US (13,26–29), Europe (30,31), and Australia (32,33). Specifically, pooled results from several studies reveal that white individuals of European ancestry have a higher age-adjusted risk of developing AMD than individuals of more recent African ancestry (13). A lower prevalence of AMD is also suggested in populations from China and Japan compared to whites (34,35). However, a pilot study has demonstrated similar prevalence of late AMD in populations from India and Europe (36). At this stage, it is unclear if these population differences are due to genetic or environmental factors, or both. Nevertheless, clear differences in disease prevalence between ethnic groups emphasize the importance of design of genetic studies (37,38).

GENETIC STUDIES

Dissecting the genetic basis of AMD using linkage analysis has presented several challenges, particularly, because of the difficulty in collecting large multi-generational families or even small pedigrees with multiple affected sib-pairs that are more readily available for the study of diseases with an earlier age of onset. Some of the early suggestions of genetic predisposition originated from familial aggregation studies. For example, a high concordance of disease phenotype was observed in monozygotic twins (11,39–41). A higher incidence of AMD was also reported in first-degree relatives of affected probands versus controls (10,42). Overall, siblings of individuals with AMD have a three to six-fold increase in disease risk (10,42,43). These initial studies established the need for further genetic evaluation of AMD.

Linkage analysis

Genetic linkage studies search for regions of chromosome that are shared between closely related affected individuals. Since close relatives share relatively long stretches of chromosome, linkage studies can survey the whole genome with only a few hundred micro-satellite markers or a few thousand SNPs. Such analyses have proven extremely effective in the dissection of Mendelian traits (44). Although the results of linkage studies for other complex diseases have been relatively disappointing (45), such investigations have overall been quite successful for AMD. The first report of linkage in a large family (10 affected individuals) with the dry form of AMD exhibiting autosomal dominant inheritance identified a genetic locus (*ARMD1*) at chromosome 1q25–q31 (LOD score 3.0) (46). As large AMD families are difficult to obtain due to the late age of disease-onset and their analysis may be complicated by phenocopy effects, the majority of subsequent linkage studies utilized the affected sib-pair or relative-pair design; these investigations have implicated several regions of the genome as harboring susceptibility loci with potentially major or minor contributions to AMD (Fig. 2) (47–55). The chromosomal regions at 1q31–32 and 10q26 were identified in several independent studies and confirmed by meta-analysis of six datasets (56). As noted below, these regions harbor the largest effect susceptibility variants for AMD, identified to date.

Association studies

Contrary to linkage studies, which entail only a coarse measurement of genetic variation, association analysis requires more detailed measurements with hundreds of thousands of markers to cover the genome (1,57,58). Due to technical limitations, until recently, genetic association studies have been limited to the study of candidate genes. Even within these limited regions, most association studies generally examined only a subset of all genetic variants, making it difficult to interpret negative results.

For macular degeneration, the first association studies explored the genes associated with rare monogenic macular diseases, whose clinical phenotypes overlap with AMD but typically have an earlier age of onset (59). These genes included *RDS/peripherin* (associated with retinitis pigmentosa, adult-onset vitelliform macular dystrophy, butterfly dystrophy, and bulls-eye maculopathy) (60), *TIMP3* (mutated in Sorsby's Fundus Dystrophy) (61), *EFEMP1* (responsible for Doyne Honeycomb retinal dystrophy) (62), *VMD2* (for Best's Macular Degeneration) (63,64), and *ELOVL4* (associated with Stargardt-like macular dystrophy)

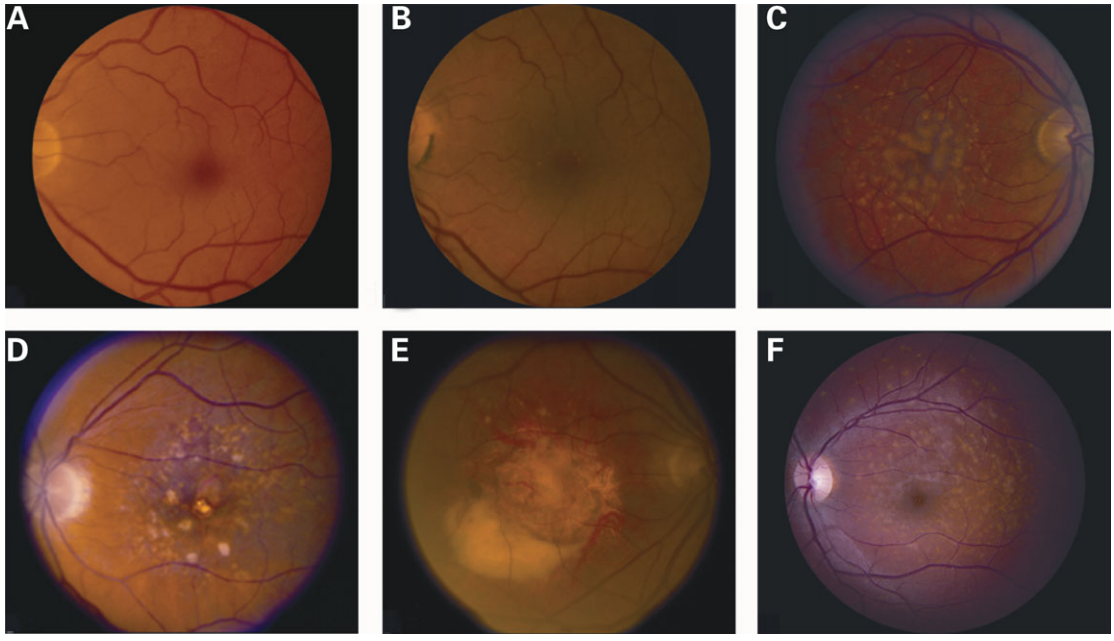

Figure 1. Fundus pictures of: (**A**) Normal, 74 year old man, (**B**) 66 year old woman with few small drusen and RPE changes, (**C**) 71 year old male with extensive soft drusen, (**D**) 87 year old woman with GA of the RPE, (**E**) 75 year old woman with disciform scar due to previous neovascularization, and (**F**) 15 year old female with pisciform flecks associated with Stargardt's macular degeneration.

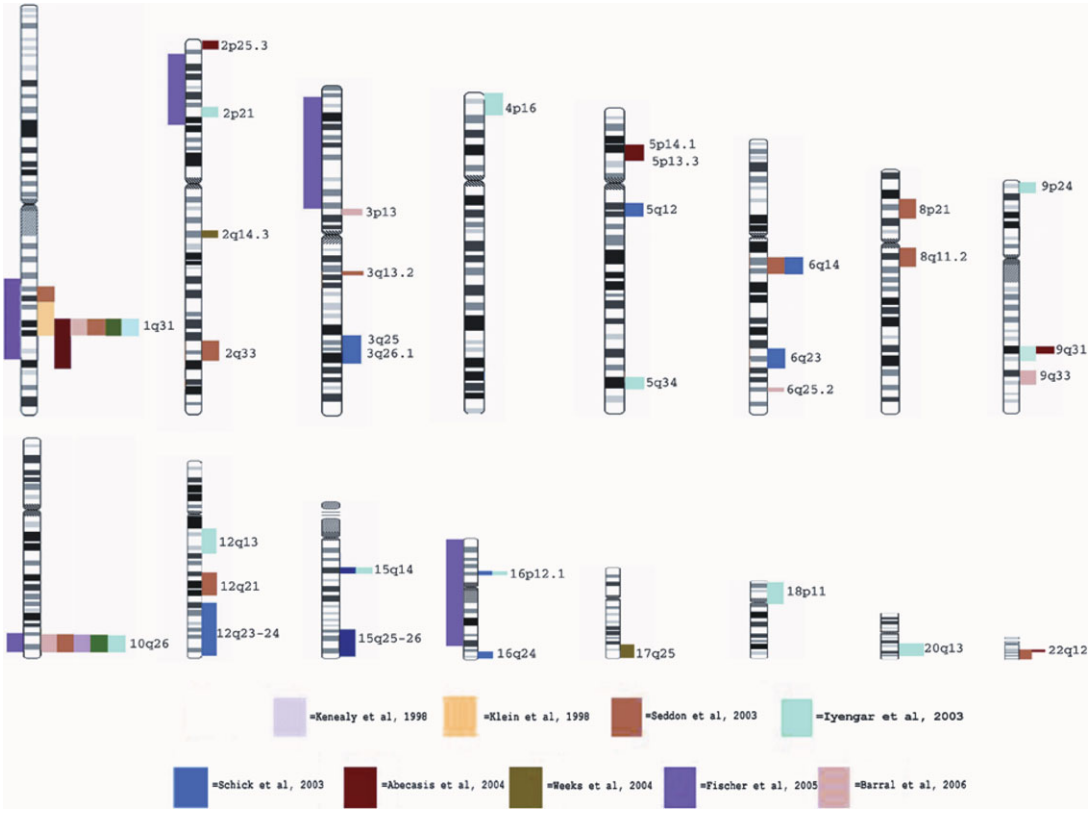

Figure 2. Compilation of results of previous linkage studies, showing chromosomal regions harboring potential AMD susceptibility loci.

(65). To date, these studies have not yielded any striking genetic associations with AMD. However, with advances in genotype and re-sequencing technologies that allow genetic association studies to examine larger numbers of individuals in greater detail, we may need to re-assess the impact of these genes on AMD.

Motivated by phenotypic similarities between Stargardt disease and AMD (Fig. 1F), multiple association studies have been performed on the gene responsible for the majority of cases of Stargardt disease, the *ABCA4* gene. Several of these have indicated an association of AMD with certain missense changes in *ABCA4* (notably D2177N and G1961E) (66,67), although there are also negative reports (68–70). At this stage, the *ABCA4* variants do not seem to make a major contribution to AMD susceptibility.

Among candidates examined in single gene studies, *APOE* exhibits the clearest association with AMD. *APOE* is involved in transport and metabolism of lipid and cholesterol and in the response to neuronal injury (reviewed by Mahley and Rall, 71). *APOE* has three common alleles, ε2, ε3 and ε4. Initially, two studies reported a reduction in the frequency of the ε4 allele in patients with AMD compared to controls, suggesting a protective effect (72,73). In addition, ε2 allele frequency was increased in AMD patients compared to controls (72). The association between *APOE* and AMD has now been replicated by several independent reports (74–76) though at least in one instance no association was obtained (77). Our meta-analysis of published studies provides relatively strong evidence of association between *APOE* ε4 allele and AMD susceptibility (Table 1). These findings differ somewhat from those of a previous meta-analysis, which analyzed pooled data across studies (78). Meta-analysis, rather than analysis of pooled data, is more appropriate when allele frequencies differ across populations.

Chromosomal regions at 1q32 and 10q26

A pioneering discovery was made by Josephine Hoh and colleagues when they executed a genome-wide association study with ∼100 000 SNPs in a small case-control sample; the results of this initial scan and their subsequent follow-up identified strong association between Y402H variant in the Complement Factor H (*CFH*) gene and increased risk of AMD (9). Concurrently, other groups obtained similar results using distinct approaches and replicated the findings (9,79–82). A meta-analysis combining results from multiple association studies of *CFH* and AMD indicate that heterozygote carriers of the risk allele have a 2.5-fold increase in developing AMD and homozygous carriers have a six-fold increase in developing AMD compared to the non-risk allele (83). Again, as noted in Table 1, the consensus of studies published to date provides compelling evidence for association between this SNP and AMD in populations of European descent.

While initial studies of the association between *CFH* and macular degeneration focused on the Y402H variant, recent investigations have examined the region more broadly. For example, Li *et al*. (84). evaluated 84 polymorphisms in and around *CFH* and demonstrated that 20 of these exhibited stronger association with disease susceptibility than the Y402H variant. Furthermore, no single SNP itself accounted for the contribution of the *CFH* locus to AMD. Instead, multiple polymorphisms defined a set of four common haplotypes (two associated with disease susceptibility and two protective) and multiple rare haplotypes (associated with increased susceptibility in aggregate). These results suggest multiple susceptibility alleles in the region, with non-coding *CFH* variants playing a key role in determining disease risk. These studies were confirmed in a companion paper, which also showed that non-coding variants in and around *CFH* appear to impact AMD independently of the Y402H variant (85). Further complexity came from the association of a deletion in *CFH*-like nearby genes (*CFHR1* and *CFHR3*) with disease susceptibility (86). Overall, the current data suggest that identifying causal variants in a complex disease may be quite challenging and that, potentially, regulatory variants may have effects that are as important—or perhaps even more important—than the coding variants or loss of function mutations that are generally associated with Mendelian disorders.

The strong association between *CFH* and AMD sparked renewed interest in the complement pathway. It is now clear that polymorphism in the *C2* and *BF* genes are also associated with disease (85,87) (unpublished data from our lab; Table 1) and it is tempting to speculate that careful assessment of other complement genes will uncover further novel associations.

Similar to the 1q32 region, chromosome 10q26 shows convincing evidence of linkage both in individual studies (54) and in a meta-analysis of several published reports (56). Fine-mapping efforts by a number of groups have yielded convincing evidence of association at two neighboring genes, *PLEKHA1* and *LOC387715* (88–90), which has been replicated (85). More recently, a genome-wide association scan also provides evidence of association between AMD susceptibility and this region (91,92), and implicates another gene, *HTRA1*, in AMD pathogenesis. These three genes are in linkage disequilibrium with each other, and association to this cluster has now been replicated in several studies (93–97) (Table 1). In an attempt to disentangle the relationship between polymorphisms in the region and AMD susceptibility, we recently examined 45 SNPs in the region (98). In contrast to fine-mapping efforts within the *CFH* locus (84) suggesting multiple susceptibility variants, our data show that a single coding variant in the *LOC387715* gene (now called *ARMS2*)—rs10490924—can account for the association between other SNPs in the region and macular degeneration. All other examined variants revealed significantly weaker association and could not account for the effect of rs10490924. The data illustrate the challenges in interpreting association study results when the implicated region includes multiple genes in linkage disequilibrium or multiple functional candidates. It is tempting to speculate that the identity of the gene responsible in the 10q26 region will be further elucidated by future association studies that implicate *PLEKHA1*-like, *LOC387715*-like or *HTRA1*-like genes in disease susceptibility.

To date, variants in the *CFH* region at chromosome 1q32 and in the *PLEKHA1* / *LOC387715* / *HTRA1* region at 10q26 have demonstrated the strongest replicable association with AMD. Variants in the *APOE*, *C2* and *BF* genes also show replicable, but smaller, association with AMD across studies and contribute to disease susceptibility. The results of several additional reports [e.g. *CST3* (99), *CX3CR1* (100), *TLR4* (101), *fibulin 5* (102), *VEGF* (103)] are encouraging; however, in our opinion, none of these have achieved the

Table 1. A summary of conclusions from meta-analysis of established associations (three or more published reports) between AMD and genetic variants

Gene	Polymorphism	Total studies	Total (*N*)	Allele frequencies			Odds ratio	Meta-analysis (*P*-value)	References
				Allele	Cases	Controls			
CFH	rs1061170 (C/T)	14	10 930	T	0.435	0.639	2.00	$<10^{-100}$	(9,79,82,85,90,96,117–123)
LOC387715	rs10490924 (G/T)	8	8473	T	0.420	0.207	2.62	$<10^{-100}$	(85,88,97,98,117,124,125)
C2	rs9332739 (C/G)	4	4184	G	0.977	0.943	2.42	1.0×10^{-12}	(85,87) + our own unpublished data
C2	rs547154 (A/C)	4	4162	C	0.949	0.892	2.20	6.8×10^{-10}	(85,87) + our own unpublished data
BF	rs4151667 (A/T)	4	4197	T	0.974	0.942	2.20	9.5×10^{-11}	(85,87) + our own unpublished data
APOE	–	8	4290	ε2	0.097	0.076	1.33	0.042	(72,73,75–77,126–129)
				ε3	0.808	0.784	1.28	0.00024	
				ε4	0.095	0.152	0.60	1.7×10^{-11}	

level of evidence required to produce broad scientific consensus.

FUTURE DIRECTIONS

A complete dissection of the genetic basis of AMD

Siblings of individuals with AMD have three to six-fold higher risk of disease compared to individuals from the population at large. Individually, the genetic variants at the chromosome 1q32 (*CFH*) and 10q26 (*LOC387715/ARMS2*) regions correspond to an increase in risk to siblings of only ∼1.2 to 1.6-fold (84,98). It is very likely that additional susceptibility loci and variants remain to be identified, and several promising approaches are now available to do so. Using new high-throughput re-sequencing platforms, it will be possible to comprehensively search for new susceptibility variants in previously identified loci (104). Additional genome-wide association scans that examine larger numbers of individuals are also likely to point to new loci that were missed in earlier smaller scans—as happened in the case of Crohn's disease (6,105,106) and diabetes (4,5,8,107). Candidate gene studies that focus on those identified in the initial studies (e.g. additional genes in the complement pathway) are likely to be promising and have already resulted in some success (87). Finally, it will be possible to take advantage of the ability to examine large numbers of individuals to carefully evaluate the role of gene–gene and gene–environment interactions and examine their contributions to disease risk.

Genome-wide association

In our view, one step that is likely to lead to additional AMD susceptibility variants will be to undertake genome-wide association studies using higher density panels that provide better coverage of the genome (108) and that examine larger number of individuals. Although larger sample sizes will always provide more power and improve the chance of new discoveries, one cost-effective option is to use a few large case-control cohorts for initial screening of 100 000s of variants, followed by detailed examination of the positive genomic regions in additional cohorts (109). Such large genome-wide scans will have profound impact on revealing a more complete genetic picture of AMD susceptibility, as demonstrated recently by 500K SNP examination of 17 000 genomes evaluated for seven common diseases (6).

Re-sequencing of selected regions

Genome-wide association studies are designed to identify common SNPs that may only increase the risk of disease by a modest amount. Since they are common, these variants can nevertheless explain a substantial fraction of disease risk in the population. However, many variations will be missed in such scans, especially rare ones that are not well tagged by the common variants, which account for the bulk of SNPs in commercial genotyping panels. Identification of rare variants with impact on disease susceptibility can be accomplished by re-sequencing the associated gene regions in a large population. This approach has been successfully used for finding coding variants in the adipokine gene that is associated with plasma triglyceride levels (110). The targeted population re-sequencing strategy could help identify genetic variants associated with AMD if it is applied to known susceptibility loci, such as the regions surrounding *CFH* and *LOC387715/ARMS2*, and other promising genomic regions (such as the genes in the complement pathway or HLA region).

CONCLUSIONS

Further dissection of genetic susceptibility and the possible interactions between variants and environmental factors (such as smoking and nutrition) will be essential for elucidating mechanisms of disease pathology. Association studies have provided valuable insights into the general location of genetic differences that influence susceptibility to AMD. Currently, we can confidently point to variants in the *CFH* region (at chromosome 1q32) and in *LOC387715/ARMS2* (at chromosome 10q26) among the major contributors. A role in disease susceptibility is also strongly supported by the available evidence for variants in the *APOE* and *C2/BF* genes. Many other genetic variants have been implicated but only in a small number reports, and a definite conclusion about their impact on disease susceptibility is not yet possible. Nevertheless, with all the genetic findings, it may soon be possible to provide pre-symptomatic diagnosis with reasonable accuracy, leading to better disease management strategies for high-risk individuals.

We must, however, mention three points of caution and/or consideration. (i) We should be aware of the difference between susceptibility and causality. For complex diseases, association (even strong) of gene variants to disease does

not represent a causal relationship as the presence of no single sequence variation can lead to clinical pathology. A number of individuals carrying high-risk Y402H allele of *CFH* and/or other haplotypes may never develop macular degeneration phenotype. (ii) We still have no clear understanding of the early steps in disease manifestation. Numerous studies indicate RPE as the primary site of disease initiation, with death of photoreceptors caused by RPE dysfunction selectively in the macula (111). Oxidative stress, inflammatory pathways, mitochondria-associated cellular processes have also been implicated in AMD pathogenesis (112–114). Animal models are required to delineate the underlying pathway(s) and discover treatments; several mouse models manifesting at least a part of the AMD disease spectrum have been reported (115,116). Further investigations are necessary to correlate risk or protective variants in associated genes to AMD pathology. (iii) Like other complex diseases, the environment is expected to play a key role in triggering AMD. We are beginning to decipher the role of some of the factors (such as smoking); yet, much work remains. A better assessment of gene–environment interaction will require larger well-phenotyped AMD population cohorts and allow opportunities for comprehensive planning of disease prevention and treatment.

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