Molecular genetic studies of age-related maculopathy (ARM), including family-based linkage studies and case-control association studies, have yielded valuable insights into the risks of developing this condition and potential disease-causing mechanisms. Variants in the complement factor H gene and LOC387715 have consistently been shown to be major risk factors for ARM. Additional genes, and environmental, behavioral, and dietary factors, also play a major role in ARM pathogenesis. The present studies are a starting point toward our understanding of the causes of ARM and for future therapeutic studies. As clinicians, we can already begin to use our knowledge of ARM genetics to counsel and care for our patients at risk.

Age-related macular degeneration (AMD) is the leading cause of irreparable vision loss in the elderly population. With the aging of the US population, it is expected that the advanced forms of this condition (wet or exudative AMD and atrophic AMD) will have an increasing effect on quality of health, require an increasing share of health care dollars to treat the acute development of choroidal neovascular membranes, and have serious societal consequences from the vision loss associated with wet and atrophic AMD. Even with the advent of new anti-vascular endothelial growth factor therapies for wet AMD, there remains the challenge of preventing the development of AMD and avoiding the onset of end-stage disease, rather than trying to intervene when vision has already been compromised. Several models of pathogenesis have been explored by characterization of tissue changes in AMD-affected eyes, and from studies of cells in culture and the use of possible animal models. However, with the realization that genetic factors play a major role in the risk of developing AMD, several investigators have used molecular genetic approaches toward complex diseases to identify genetic variants that are contributory to AMD.

To study AMD as a genetic disease, it has been critical to have a clinical definition of the disorder that is amenable for genetic studies. First, one has to consider how to handle evidence of mild macular degeneration that precedes vision loss. It is preferable to use the distinction of “mild” compared with “early” stages of AMD, because the latter term presumes that the condition will be progressive. The same degree of severity of findings in a young individual (<50 years) compared with an elderly person (>70 years) may not reflect an equivalent likelihood of disease progression. Most molecular geneticists use an expanded clinical definition of AMD that includes the full clinical spectrum of the condition (including presymptomatic disease) and use the term age-related maculopathy (ARM). For this review, we

Author Affiliations: Departments of Ophthalmology, The David Geffen School of Medicine at UCLA, Los Angeles, Calif, and University of Pittsburgh School of Medicine and Graduate School of Public Health, UPMC Eye Center, Pittsburgh, Pa. Dr Gorin is now with the Jules Stein Eye Institute, Los Angeles.
prefer to use this term because it encompasses the genetic studies that are done for all levels of macular changes. Second, one has to decide what assumptions regarding the genetics of the condition can be based on the clinical findings. While it is common to use clinical phenotypes to characterize rare classic mendelian genetic conditions, we know that the same clinical findings in separate families can be the result of mutations in different genes (genetic heterogeneity) and that the same mutation in a gene can give rise to different clinical findings among multiple individuals (variable expressivity). This diversity of clinical findings is especially true for complex genetic disorders, which are influenced by variants in multiple genes, and by interactions with environmental and dietary factors. Thus, one must be extremely cautious in using specific subsets of clinical findings to define subtypes of ARM with the intention of reducing the complexity of the genetics. However, the clinical characterization of ARM cases can be used to address genotype-phenotype correlations, which reflect the extent to which specific genetic variants influence the likelihood of observing different clinical findings, such as the type of drusen, pigment epithelial detachments, choroidal neovascular membranes, and/or geographic atrophy.

With the present genetic studies, one finds a variety of ARM definitions, including discrete categories of affected and unaffected states and grading systems that allow for quantitative trait analyses. These differences may partially account for why some genetic linkage studies identify some loci that have not been replicated by other studies. On the other hand, when these diverse studies identify the same genetic loci and variants as contributors to ARM or AMD, it actually reinforces the plausibility of the relationships because every clinical definition has the potential of an ascertainment bias. Such a bias is potentially minimized by the multiple approaches and ARM definitions. One of the challenges in studying ARM is whether we can separate out those phenocopies that are conditions that clinically seem similar to ARM from the “real” disease. In some cases, the clinical history or early findings can guide us, but until we understand the causes underlying ARM, we cannot be sure of the limits of its clinical definition. This is one way in which our growing knowledge of the genetics of ARM may eventually lead to a redefinition of the clinical condition (such as whether one can have ARM in the absence of clinically evident drusen). Another key objective from the clinical characterization of the condition is whether genetic variants can determine if an individual will progress to either geographic atrophy or the development of a choroidal neovascular membrane. At this point, the answer is unknown, but it is important to recognize that, at best, the answer will never be a clear-cut “yes” or “no,” but rather a set of probabilities.

During the past few years, molecular genetic studies based on family linkage analysis and case-control association studies have transformed our understanding of ARM. The potential role of family history as a risk factor has been recognized for more than 30 years; however, there has been considerable debate as to the extent that genetic factors are critical to ARM pathogenesis. Twin studies and segregation analyses reinforced the importance of genetic risk factors for ARM, but these studies could not establish how many or which genes potentially were involved with ARM. It seemed that within some ARM families, a single major gene could be responsible for most of the inherited risk (a review was previously published). At the same time, there were concerns that so many different genes could be involved that no molecular genetic method would succeed in detecting any with a reasonably sized cohort of ARM families or case-control groups. Additional concerns included how to handle cases of ARM with intermediate severity and how to distinguish those individuals with minimal or mild findings and those who are likely to progress to more advanced disease or remain otherwise stable. Some investigators adopted a disease model based on the hypothesis that the same genes responsible for monogenic juvenile macular dystrophies (such as Best disease, Stargardt disease, North Carolina macular dystrophy, and malattia leventinese) would have common variants that would cause an older-onset macular degeneration. Similar approaches have been considered for other complex genetic disorders, such as Parkinson disease, Alzheimer disease, and atherosclerosis.

Before we discuss the clinical implications of the recent discoveries regarding the genes that have been associated with ARM, we should consider the definition of a complex genetic disorder. Most clinicians are familiar with the concept of a classic mendelian disorder, in which 1 copy of an altered gene (autosomal dominant inheritance) or 2 copies of altered genes (autosomal recessive inheritance) are necessary and sufficient to produce a disease phenotype. For complex genetic disorders, there can be genetic heterogeneity and interactions of variants from multiple genes. Variants in genes can confer (or reduce) risk of developing disease in much more diverse ways than simply being “sufficient and necessary.” Variants can be “necessary but not sufficient,” “sufficient but not necessary,” or probabilistic modifiers that are “neither necessary nor sufficient.” Genetic variants may interact with behavioral and environmental factors that contribute to disease risk, such that a molecular genetic variant could enhance the probability of developing ARM in a person who smokes, or these factors could act as independent risk factors. These various alternatives challenge our classic simpler concepts of causality that have dominated genetic research of rare disorders. It is crucial that we appreciate these issues as we attempt to interpret the latest research results and consider how to use knowledge of these variants to counsel patients and family members with respect to ARM risk.

ARM, in addition to being a complex disorder, is also a common condition, increasing in frequency with advancing age. The genetic models of common disorders tend to fall into 2 major categories: either a “few”
common variants for a common disease or many “rare” variants for a common disease. In the first category, one envisions that there is a variant that is relatively common in the population (presumably because of a founder effect and perhaps some selection pressure for propagation of the variant) that conveys a significant degree of risk to the population. Association studies are a powerful tool for identifying such variants. In contrast, the rare variant model is based on the concept that many independent mutations have arisen in 1 or more genes and all of these variants contribute to the risk of developing disease within the population. In this situation, association studies are potentially problematic because each variant contributes to a relatively small percentage of the cases. Without sufficient numbers of cases and controls, one might not observe statistically significant differences. However, if each different variant within the same gene is capable of having a major effect on disease risk, then family linkage studies may show positive signals (even in the absence of an allele-specific association) because these linkage studies ask how often the same genetic material is shared by affected family members, regardless of which variant within that DNA is responsible in a given family.

In reality, most common, complex, genetic disorders do not reflect a single model, but result from an amalgam of both mechanisms. Under these circumstances, the extent to which one may find common variants or multiple rare variants is based not only on the disease itself and the structures of the relevant genes but also on the particular populations that are studied. A strong founder effect may be clearly evident in one population and nearly absent in another. We may identify some ARM genetic loci by linkage studies that will not be readily amenable to discovery by single nucleotide polymorphism–based association studies, and it is possible that association studies can identify true risk-associated variants that might not be detectable by some family-based studies. One such example is the association of the complement component 2/factor B locus with ARM\(^{10}\) that was not observed in any of the family-based linkage studies. This apparent lack of a corresponding linkage signal can potentially be explained by the observation that the most strongly ARM-associated alleles for this locus were protective and would not be easily detected in family studies based on the evaluation of affected sib pairs. Also, association studies can often detect genes of smaller effect than can linkage studies.

Studies of ARM in multiple populations may lead to replication of some genetic variants and unique discoveries as well. Consequently, multifaceted genetic approaches and the integration of biological pathways are crucial for the construction of a model of disease pathogenesis. Given the complexity of the potential interactions and the vast range of genetic models that might account for the disease, it becomes clear why so few common complex genetic conditions (such as glaucoma and myopia) have yet to yield their genetic secrets. At the same time, it is all the more remarkable how successful the recent studies of ARM have been.

**SUMMARY OF GENETIC FINDINGS**

The prior genetic studies of ARM that preceded the present linkage and association studies are summarized elsewhere.\(^9\) An extensive compilation of the recent studies discussed in this article has been recently published.\(^11\) The loci reported by multiple linkage studies are summarized in a meta-analysis study by Fisher et al\(^12\) and the genetics in an ARM review.\(^13\) Some of these loci have been repeatedly detected even with different disease models and analytical methods. In contrast, there are several loci that have been reported in 1 or 2 studies. Some may represent false-positive association signals, while others may be specific to the manner in which the macular degeneration was defined and/or analyzed. The replication of linkage signals requires a considerably larger sample size than the original cohort used for the initial discovery, and nearly all of the present linkage studies are insufficiently powered to test all of the reported loci, some of which may have only a limited contribution to the risk of developing ARM. Given the large genetic intervals that are implicated by these linkage studies, association studies are essential to test potential candidate genes. The first dramatic success of association studies for ARM was the discovery of a variant in the complement factor H (CFH) gene by genomewide and focused regional genotyping using single-nucleotide polymorphism.\(^13\-15\) It is valuable to test whether reported associations within these genetic intervals actually account for the linkage evidence that has been reported. This has only been done for CFH and LOC387715.\(^16\-17\) In the initial report\(^16\) on LOC387715, the genetic analyses could not distinguish whether LOC387715 (within a possible promoter region of HTRAI (a serine protease gene) or PLEKHA1 was the responsible gene because these genes are so close together that their variants are highly correlated (linkage disequilibrium). Subsequent studies\(^16\-19\) have reinforced the evidence that directly implicates LOC387715. Two recent articles in *Science* are implicating HTRAI as the preferred gene.\(^20\-21\) For these 2 genes, the power of the associations and the consistency of the results among multiple studies provide convincing evidence that they play major roles in the pathogenesis of ARM. These associations and the reported odds ratios (ORs) are summarized in the review by Haddad et al.\(^11\) A few of these reports have been replicated in multiple studies. Given the possibility for false-positive association signals (particularly with genomewide studies), one must adjust the level of significance to account for the number of variants (single-nucleotide polymorphisms) that are tested and use a highly stringent criterion for accepting the result. Even when an association is tested in a relatively isolated fashion (such as a candidate gene based on a biological hypothesis), one must be extremely cautious in accepting a standard test of statistical significance. One should generally view more modest association results as no more than suggestive, even when the association is with a variant that is
plausible from a biological perspective (such as the case for the TLR4 gene).

What can we infer from the association studies for CFH and LOC387715? In the case of CFH, there is a well-recognized appreciation of its role as a regulator of the alternative complement pathway. An aberration in the function or expression of the CFH protein could interfere with the essential down-regulation of the alternative pathway and lead to excessive inflammation and damage of the tissue. There is also strong histologic evidence that CFH is present in ARM-related drusen. One cannot exclude the possibility that the CFH protein could play as yet an undiscovered role in cell biology. However, the recent association of the complement component 2 factor B locus with ARM serves to strengthen the argument that we are dealing with the alternative complement pathway as a key pathogenic factor for ARM. In the case of LOC387715, we see as strong an effect on the risk of having ARM as CFH, but we have virtually no biological data to explain its potential role. The predicted protein is apparently expressed in the placenta but is present in barely detectable levels in the eye. Its function is unknown, although at least 1 gene in close proximity to LOC387715, PLEKHA1, is known to be involved in cellular immunity.

The ARM-associated ORs that have been reported from case-control association studies for the variants of CFH and LOC387715 have been remarkably consistent among the multiple studies. A meta-analysis of the present studies indicates that the risk allele for CFH has an OR of 2.4 (95% confidence interval [CI], 2.2-2.7) and 6.2 (95% CI, 5.4-7.2) in the heterozygous and homozygous states, respectively. Similarly, the risk allele for LOC387715 confers an OR of 2.5 (95% CI, 2.2-2.9) and 7.3 (95% CI, 5.7-9.4) for the heterozygous and homozygous states, respectively. In a prospective analysis conducted with individuals from the Physicians’ Health Study, a much more modest OR (which more closely estimates the true relative risk) was observed for the ARM-associated CFH variant. They reported an OR of 1.46 (95% CI, 1.05-2.04) for TC heterozygotes and an OR of 2.13 (95% CI, 1.10-4.16) for CC homozygotes, assuming a multiplicative (log-additive) model and an attributable fraction of 25% (95% CI, 1%-44%). A more recent population-based, prospective, cohort study confirmed a significant contribution of CFH alleles to AMD but also demonstrated a strong influence of smoking and the presence of systemic inflammation (as evidenced by several biomarkers) on AMD risk. The population-attributable risk for advanced ARM was 54%, but even with an OR of 1.02 for those homozygous for the high-risk allele, 18.1% of the individuals with advanced ARM did not carry a copy of the high-risk allele and 45% of the advanced cases had only 1 copy. At the same time, 45.4% and 10.7% of the individuals without any evidence of ARM had 1 or 2 copies of the high-risk CFH allele, respectively.

Genetic studies can only detect the genes (and, hence, the proteins) involved in ARM for which there are functionally significant variants. These variants may alter protein structure and/or affect transcription, RNA splicing, or RNA degradation. The detection of such an association can be with the actual functional variant and with genetic variants that are in strong linkage disequilibrium with the locus. Genes, which play an integral role in the pathogenesis of ARM, such as a molecular target in the Bruch membrane, can be highly conserved and invariant and, hence, not detectable by either linkage or association studies. These genetic targets are necessary but not sufficient for the development of disease. They establish a set degree of risk for the entire species, but they will not be detected by human genetic studies. However, we can search for these components of ARM pathogenesis based on their biological relationships with other genetic factors and validated with animal models of the disease.

The present genetic studies can identify variants that confer increased risk of developing ARM. We can identify variants that confer decreased risk of developing ARM but only by association studies (case-control or family based) or by discordant sibpair linkage analyses. The determination of risk-reducing alleles is more challenging because of the difficulty in establishing that someone is truly unaffected. For discordant sibpair studies, the unaffected individuals need to be carefully ascertained and usually must be considerably older than the age of onset of most of the affected individuals. In every control group, there is a small percentage of individuals with no evidence of ARM at the age of ascertainment and yet who later develop the condition. These individuals may lower the strength of an association between case and control cohorts, but should not cause a false-positive association.

Association studies are generally predicated on a sufficient founder effect that one can observe a significant difference in the prevalence of a variant in the affected individuals compared with the controls. This is true for CFH and LOC387715, but other genes may have numerous variants, each potentially conferring some degree of risk. It is possible to observe a positive association in the absence of a founder effect if one is evaluating disease-causing variants that have arisen independently. Family linkage studies can coalesce these variants to create a detectable signal, but if they contribute to a minority of families or have a weak effect, the linkage studies may lack sufficient power. Meta-analyses of multiple studies can provide clues but not definitive results. Association studies in the absence of a strong founder effect can make it difficult to achieve statistically significant results, and genomewide association scans test so many potential associations that numerous false positives can easily obscure a true positive.

We can summarize the results of all of these molecular genetic studies with the following statements.

- Age-related maculopathy is a complex disorder in which multiple genetic variants contribute to the risk of developing the disease. In addition, we know that external fac-
tors, such as diet and smoking,\textsuperscript{25} also contribute to disease susceptibility. There have been some reports of interactions between smoking and specific genetic variants, but these have not yet been replicated.

- The present genetic studies suggest that ARM is much less heterogeneous than previously thought. While multiple genes may play varying roles in different families and individuals, there are probably common pathogenic pathways and a set of conditions that are intrinsic to the disease.
- There is no evidence to suggest that familial ARM is any different than sporadic ARM.\textsuperscript{26} Based on the concordance of case-control and family-based association studies, the contribution of genetics seems to be comparable for those with and without family histories of the disease.
- Juvenile macular dystrophies, such as Stargardt disease, Best disease, maculitis leventines, pattern dystrophy (ie, foveomacular dystrophy) (RDS/peripherin), and North Carolina macular dystrophy, play at best a minor role in the cases of late-onset macular degeneration.\textsuperscript{27-29} This revelation reinforces the importance of better clinical definitions of ARM that will allow us to distinguish these other conditions, which share some phenotypic features. This is also true of other causes of macular degeneration, such as ocular histoplasmosis syndrome, punctate inner choroidopathy, and central serous chorioretinopathy. We need better diagnostic tools to recognize these less common causes of central vision loss and determine if they require different therapeutic approaches.
- It remains unclear whether other macular degeneration processes, such as polypoidal choroidal venules, represent distinct entities from the ARM primarily observed in the white population or alternative manifestations of a related degenerative and inflammatory process.
- The genetics of ARM have not provided strong evidence regarding genetic determinants that are specific for the progression to atrophic disease and/or exudative disease. The associations with \textit{CFH} and \textit{LOC387715} apply to exudative and atrophic forms of ARM.
- The role of apolipoprotein E seems to be real, but the extent of its role is unclear and may again be related to exogenous factors as well.\textsuperscript{33,36}
- Based on the positive results for \textit{CFH} variants, other potential regulators of the alternative complement pathway are being tested as candidate risk factors for ARM by association studies. Positive results have been reported for complement component 2 and factor B. While one group\textsuperscript{10} has proposed a risk assessment model based on alleles for \textit{CFH}, complement component 2, and factor B, there are insufficient data to establish a genetic risk assessment model for ARM that can be used clinically.

### GENE-ENVIRONMENT INTERACTIONS

There has been considerable interest in environmental and dietary factors\textsuperscript{37-49} that may contribute to the risk of developing ARM. Multiple studies have shown a significant risk attributable to smoking.\textsuperscript{44,45} While there have been several population-based studies that have suggested associations of ARM with low serum levels and/or intake of macular carotenoids (such as lutein and zeaxanthin),\textsuperscript{40,50-55} Like many risk factors, one can clearly identify individuals with high-risk characteristics who do not go on to develop ARM and others who have progressive disease with no evidence of such external risk factors. Thus, it is tantalizing to consider if there are specific interactions of genetic variants with these risk factors. The results with the known genetic factors and smoking and diet have been tantalizing but unproved. An interaction of smoking with a locus on chromosome 10 (\textit{GRK/RGS}) was reported,\textsuperscript{16} but has not been replicated. Another group\textsuperscript{19} reported an interaction of smoking exposure with \textit{LOC387715}, but this observation has not yet been successfully replicated. When the Y402H variant of \textit{CFH} was initially reported to be associated with ARM risk, several groups cited the effects of smoking on complement levels as supportive evidence for the role of \textit{CFH}. This is reasonable speculation, but, to date, there has not been any demonstrable interaction by genetic testing methods.\textsuperscript{56} The most recent study by Seddon et al\textsuperscript{57} for \textit{CFH} variants, smoking, and body mass index in the Age-Related Eye Disease Study cohorts suggested that each of these risk factors acted independently of each other, thus providing the possibility that one can potentially lessen a significant component of ARM risk by behavioral modifications. However, the relative independence of these risk factors also would suggest that it is better for all individuals to engage in risk reduction behavior (because the amount of benefit is comparable) rather than trying to use genotyping to focus one’s efforts on a more selective fraction of the population. In contrast, if we found a genetic variant that interacted with smoking such that these individuals’ risk of developing ARM while smoking was substantially greater than that of others, then genetic testing might be warranted to provide these individuals with additional incentives and resources to discontinue smoking.

Statins\textsuperscript{58-61} and nonsteroidal anti-inflammatory drugs\textsuperscript{62} have been inconsistently reported to be associated with lowered risks of ARM, possibly because of the antioxidant effects of statins\textsuperscript{63,64} and/or the modulation of the inflammatory response by the nonsteroidal anti-inflammatory drugs. Statins also have a major effect on cholesterol metabolism, and this may represent another mechanism for affecting ARM risk, given the multiple reports of apolipoprotein E variants associated with ARM risk. Lipid and cholesterol have been localized within ARM-related drusen deposits in the retinal pigment epithelium and Bruch membrane. Replication of these associations is lacking, although it is tantalizing to search for such relationships given the possibility of modifying one’s risk of developing ARM. One can speculate that genetic factors may modify the potential benefits of these medications, making them relevant for only selected subsets of the ARM at-
risk population. To my knowledge, no studies have been done that have evaluated these medications within a genetics context. These will be difficult studies to perform because the number of potential factors greatly increases the case-control sample sizes that will be required to test for such interactions.

CLINICAL RELEVANCE OF PRESENT KNOWLEDGE

The clinical goals of genetics research for ARM are as follows: (1) to identify the pathogenic mechanisms of the disease so that preventive therapies can be developed and (2) to identify individuals at risk for developing ARM so that preventive therapies can be appropriately and cost-effectively implemented to lower the probability of developing disease. The results of the present genetic studies are exciting and dramatic, but they only provide a beginning. There are linkage signals that have been observed in 1 or more studies that seem to be relatively weak but could represent true positives (or false positives) (Haddad et al. 2001 provide a summary). There is the possibility of conditioning existing linkage studies using our present knowledge of major associations, such as CFH and LOC387715, to allow us to strengthen the detection of other loci. However, most of the present ARM linkage and case-control association studies are too small to have sufficient statistical power to evaluate complex genetic models.

In linkage studies, one uses statistical variables that reflect the probability that the disease locus is closely linked to 1 or more genetic markers based on 1 or more inheritance models (a parametric approach) or the degree to which sharing of a locus among affected individuals within a family is not accounted for by chance (a non-parametric approach). These statistics are affected by several factors, including the appropriateness of the genetic model, the sample size, and the strength of the effect of the particular locus on the disease itself. A low LOD (logarithm of odds) score may reflect weak evidence of linkage, a relatively weak effect of the locus on the disease, or the fact that the study does not have sufficient power to show a strong effect. A high LOD score provides more convincing evidence that a disease-related gene exists within a locus but it does not tell us how important the variations in that gene are with respect to the disease risk. Typically, we rely on 2 measures, the OR and the attributable risk, to give us some estimates as to the impact of a genetic variant on a disease. Most clinicians are somewhat familiar with these concepts from other genetic, environmental, and dietary association studies, which use the comparisons of cases and controls. However, the OR can be misleading in genetic studies of common disorders because it usually represents an upper bound of another measure, the relative risk, which is what people generally think about with risk factors. An OR provides a measure of the difference in the frequency of a risk allele between case and control groups. For a common disorder, such as ARM, this OR is usually not the same as the relative risk, which is the increased likelihood that a person will develop ARM if the person has the high-risk allele compared with individuals who have the “normal” or low-risk allele(s). Relative risk cannot be measured from case-control association studies and requires that one prospectively monitor a group of people for the development of disease with knowledge of their genotypes and/or exposures. Similarly, the population-attributable risk that is calculated from a case-control association study reflects the prediction of how much of the disease would be eliminated from the case-control population if the high-risk genotype were not present. However, that is not the same as saying that a certain percentage of AMD is caused by a specific variant. This is why we see reports of attributable risks of 40% to 60% for CFH or LOC387715 variants and yet the 2 genes together do not constitute 100% of the risk of developing ARM. Only a few of the present studies have been designed to provide accurate relative risk assessments and population-attributable risks for genetic variants associated with ARM. We can make some initial estimates from population-based longitudinal studies, such as the Beaver Dam and the Blue Mountain Eye studies, but the relatively low percentages of individuals in these populations with advanced ARM are still limiting factors. These population-based studies are essential for gathering the kind of risk assessment information that will be crucial for clinical genetic counseling and decisions regarding the appropriateness of genetic-based diagnostics and care. These distinctions between ORs and relative risks are important for the clinician, because the inappropriate interpretation of ORs to calculate clinical risk can be misleading. As previously noted, the prevalence of the high-risk CFH allele (in a heterozygous state) in the control population is roughly comparable to that in the affected group.

A therapeutic strategy solely directed at reducing the impact of the high-risk CFH variant is probably overly simplistic. Given the high frequency of the high-risk allele in the general population, we have to consider the possibility that such an allele may have been under positive selection for other circumstances (such as protection from infection in younger individuals) and that there may be adverse consequences to negating its effects. The previously described studies clearly illustrate that behavioral and environmental factors, such as smoking and diet, can have a major effect on ARM risk, especially for those who have elevated risk from genetic factors. The population-based data show that having 1 or even 2 copies of the high-risk CFH allele is neither sufficient nor necessary for developing advanced ARM. Just as I have tried to illustrate that we need to redefine our definitions of genetic causality for complex genetic disorders, so too do we need to approach prevention therapies in a more integrated and complex approach that balances the risks and benefits of genetic testing with the effectiveness of multiple interventions for risk reduction.

Additional genomewide association studies are under way. The Age-
Related Eye Disease Study researchers will be releasing data on such studies based on 200 controls, 200 moderate ARM cases, 200 exudative cases, and 200 atrophic cases within the next few months. The challenge with these results will be how to prioritize the “signals” that do not dramatically rise above the noise. One can condition these results with the results of the linkage studies and/or the biological models that have been suggested by other studies.

The optimal targets for drug therapy to prevent ARM may not be the genes for which variants are known, but the other proteins with which those gene products interact. Other pharmacologic targets may include RNA and/or proteins that affect gene expression at the transcriptional or posttranscriptional processing levels. Attempting to modulate the activity of CFH in individuals with a high-risk ARM variant may be a reasonable pharmacologic strategy, but given the body’s use of the alternative pathway for many critical functions, it may be more reasonable to target a molecule that is responsible for the tissue specificity of the degenerative process that leads to ARM. Thus, there is a need to integrate the results of the present genetic studies on ARM with hypothesis testing of other biological processes that have been implicated in ARM pathogenesis, such as lipid and protein oxidative damage and metabolism, iron metabolism, and cellular processing.

One can foresee combining genetic testing with clinical phenotyping of early disease to create more effective ARM risk assessments. Such cohorts are particularly valuable for testing preventive therapies in a rapid and cost-effective fashion. Depending on the costs and risks of preventive therapies (and on their potential general health benefits), one may need to have future genetic testing of individuals to determine if they have sufficiently elevated risk for developing ARM that they should receive preventive therapy. The threshold for such testing and interventions may be difficult to establish because it must include medical, political, social, ethical, and financial issues. If the preventive modalities are low risk and low cost (such as vitamin therapies) and one can achieve adequate population compliance, then molecular genetic screening may be inappropriate. However, if the treatment requires a costly medication or a therapy that may have adverse risks in other respects, then it may be necessary to be more selective regarding the population for treatment.

Gene therapy is an unlikely option for the preventive treatment of ARM, although some investigators are exploring if it can be used to arrest advanced disease. As a preventive therapy, one would have to consider the short- and long-term risks of the gene therapy vs the potential benefit. Depending on the potential risks and costs of the gene therapy, one would have to establish an appropriate starting level of ARM risk for a given individual based on the individual’s genetics and environmental exposures, and would have to consider the relative reduction in risk that would be feasible by modifying exogenous factors (diet, avoidance of smoking, and medications) compared with the risk reduction associated with the gene therapy with or without additional measures. There is a real need for a therapy that will address the underlying degenerative process, rather than trying to stop or control end-stage complications. Much research will be necessary before clinicians and patients can effectively address these issues. Would a person be willing to have gene therapy performed on his or her “better” eye? Would a person be willing to have gene therapy performed at a young age, before the onset of clinically apparent disease (when prevention would be likely to be most effective)?

We can already begin to use our genetic understanding of ARM to benefit our patients. By recognizing that a positive family history of ARM can significantly increase one’s risk of developing ARM,65 we can use this information to condition our recommendations for patients who show mild findings of ARM at an early age. The results of the Age-Related Eye Disease Study only apply to elderly persons with relatively advanced ARM. However, the study failed to show a benefit for those with relatively mild or minimal ARM findings, perhaps because these individuals had a low probability of experiencing progression regardless of their treatment category. The study was not designed to answer the question of whether the vitamin and mineral supplements would prevent progression in younger individuals who are at high risk for developing ARM. While one may hesitate to recommend vitamin and mineral supplementation for every patient with mild findings of ARM, one may want to consider recommending such supplements for those who have an increased genetic risk. Molecular testing for genetic variants associated with ARM is not appropriate for this risk determination. As previously noted, the ORs calculated by case-control association studies do not translate into individual risk assessments and additional prospective studies are necessary. The high-risk variants for CFH and LOC387715 are common in the population, and many of those who have 1 or more of these variants will never develop ARM. We need to continue to invest in additional genetic studies to identify and test a combination of genetic variants to achieve a sufficient level of discrimination to be clinically useful.

Submitted for Publication: July 25, 2006; final revision received September 4, 2006; accepted September 5, 2006.

Correspondence: Michael B. Gorin, MD, PhD, Jules Stein Eye Institute, 200 Stein Plaza, Room 3-310B, Los Angeles, CA 90095-7000 (gorin@sei.ucla.edu).

Financial Disclosure: Dr Gorin is listed as one of the coinventors for an application made by the University of Pittsburgh for a patent regarding the use of variants in the LOC387715 locus (and the adjacent PLEKHA1 locus) for the diagnosis and possible therapy of ARM.

Funding/Support: This study was supported by the Smith Kettlewell Research Foundation, San Francisco, Calif; grant RO1 EY0098598 from the National Eye Institute, Bethesda, Md; the Ruth and Milton Steinbach Foundation, New York,
REFERENCES


