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The genetics of age-related macular degeneration

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Age-related macular degeneration (AMD) is increasingly recognized as a complex genetic disorder in which one or more genes contribute to an individual's susceptibility for developing the condition. Twin and family studies as well as population-based genetic epidemiologic methods have convincingly demonstrated the importance of genetics in AMD, though the extent of heritability, the number of genes involved, and the phenotypic and genetic heterogeneity of the condition remain unresolved. The extent to which other hereditary macular dystrophies such as Stargardts disease, familial radial drusen (malattia leventinese), Best's disease, and peripherin/RDS-related dystrophy are related to AMD remains unclear. Alzheimer's disease, another late onset, heterogeneous degenerative disorder of the central nervous system, offers a valuable model for identifying the issues that confront AMD genetics.

INTRODUCTION

Despite numerous references in the ophthalmic literature dating more than 80 years ago [1], the genetic basis of age-related macular degeneration (AMD) has only recently received focused attention from both the ophthalmology and genetics communities. This attention has largely been due to the growing awareness of the role of genetics for a number of complex, late-onset medical disorders and the development of new tools that allow us to define the genetic loci that contribute to disease susceptibility. In this session of the AMD Symposium, we focused on the evidence that supports the genetic basis of AMD, the lessons that have been learned from the genetics of Alzheimer's disease, the strategies and methods for identifying AMD susceptibility loci, and other molecular approaches to understand the etiologies of AMD.

IS THERE A DISTINCTIVE PHENOTYPE FOR AMD?

A primary issue for genetics studies of AMD is the need for an adequate definition of the disorder. A classification system [2] that is useful for epidemiologic studies or clinical trials of AMD may not be ideal for genetic analyses. The grading of ocular pathology can provide an estimate of the severity of the disease, but does not necessarily correlate with the certainty of the diagnosis. AMD is a condition that manifests progressive changes as well as endstage forms that often obscure the underlying abnormalities. A number of disorders have similar endstage patterns of pigment epithelial atrophy or chorioretinal scarring that can mimic the diagnosis of AMD. Short of endstage disease, there is controversy as to the point at which a person has accumulated sufficient retinal pathology to warrant a diagnosis of AMD, as compared to normal aging. The Beaver Dam study demonstrated that there is a significantly increased risk that patients with soft drusen are likely to progress to advanced forms of AMD, and that small hard drusen are common and not necessarily correlated with advanced AMD [3]. However, there are clearly cases in which advanced disease (either geographic atrophy or choroidal neovascular membranes) develops in the absence of soft drusen. Do these patients have AMD or a phenotypically distinguishable form of macular degeneration? Do the endstage patterns of disease (geographic atrophy or choroidal neovascular membranes) represent different underlying etiologies for AMD? Are macular photographs a sufficient tool for documentation of AMD, or does this method of documentation overlook important peripheral retinal pathology?

Lewis et al [4,5], previously demonstrated that reticular degeneration of the pigment epithelium and extramacular drusen are closely correlated with AMD. These peripheral changes can often be identified far before there are significant macular changes and they often are found in hereditary patterns within families whose older members have advanced AMD [6]. Should these findings also be included as part of the phenotype for some families? Should age of onset and/or the presence of vision loss be included in the definition of AMD?

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The problems with the phenotype of AMD are not unlike those that confronted the investigators of Alzheimer's disease (AD). Similar to AMD, some AD cases have particularly aggressive development of dementia and early ages of onset. However, early work from Sweden [7] identified a typical course of illness for late-onset, more typical forms of Alzheimer's disease (AD). For 25 years, this approach to "positive identification" was largely ignored in the U.S., where AD was regarded as a diagnosis of exclusion-resulting in substantial phenotypic heterogeneity in the AD category. Two things changed this: First was the discovery in the 1970's that neurotransmitter defects in AD were specific, i.e., that AD is not a generalized process of neurodegeneration but is instead a more specific entity, i.e., a disease. [8] Second was the discovery by Marshal Folstein and John Breitner that the "positive identification" approach identified a form of "senile dementia of the Alzheimer type" with considerable familial aggregation [9]. The demonstration of the familial nature of "true" AD was facilitated by the development of survival analytic techniques. For a review of the genetic epidemiology of Alzheimer disease, see [10,11].

Does clinical heterogeneity correlate with genetic heterogeneity?

A second issue is whether or not the different clinical manifestations of AMD based on the presence or absence of drusen, the type of drusen, ancillary findings, the development of geographic atrophy and/or choroidal neovascular membranes can be used to distinguish different genetic forms of AMD. At least two hereditary macular dystrophies, Stargardt's disease [12-14] and peripherin/RDS-related disorders [15-18], are known to manifest several forms within families. Best's disease can have reduced penetrance and variable expressivity within families. Monozygotic twin studies of AMD have shown impressive concordance of clinical features of AMD, suggesting that within families there may be specific phenotypes [19-21]. However de la Paz and Seddon [22] have documented a wide range of AMD phenotypes in several moderate- and larger-sized AMD families. For a complex genetic disorder such as AMD, it is possible that a single altered gene may be primarily responsible for disease susceptibility, and yet other genes may modify the age of onset or phenotypic features. Thus there is little support for using clinical phenotypes at this time to subclassify AMD families, though this may be possible when one or more causative genes are identified. Just as important is the unresolved question as to the number of genetic loci that may contribute to an individual developing AMD as well as the overall genetic heterogeneity of the condition.

What is the evidence for AMD as a genetic disorder?

The cumulative evidence from twin studies, population-based segregation analyses such as from Beaver Dam [23] and Framingham studies [24] and familial aggregation studies such as that undertaken in the Rotterdam Eye Study [25] and in Boston [26] are compelling arguments for the role of genetics in AMD. However they provide only approximate estimates as to the complexity and extent of the genetics of AMD. There are relatively few series of monozygotic and dizygotic twin studies of AMD [21,27] with confirmed zygosity by genetic testing. Meyers [27] reported concordance of AMD in 23 of 23 monozygotic and 2 of 8 dizygotic volunteer, twin pairs; this included one dizygotic pair which was discordant for basal laminar drusen. Klein et al [21] noted that eight of the nine monozygotic twin pairs had similar fundus appearances and severities of visual impairment. In the ninth pair, one twin had advanced exudative AMD with vision loss in one eye, while the other had large, confluent drusen and good visual function in both eyes. Unlike Alzheimer's disease, there have been no systematic population-based surveys of twins for AMD in order to estimate the degree of heritability. However such a twin study is currently underway in an effort to avoid the potential biases in small, volunteer-based samples and to provide a better estimate of the heritability of AMD and the role of environmental factors [28,29]. There have been four such studies for AD [30-33]. Three studies included subjects of all ages, specifically including those that are most typical for AD onset; one was in a restricted population of younger men. The former three suggested that 60-75% of the population variability in AD susceptibility can be attributed to genes. The last found a much lower heritability. In interpreting these findings, one should remember that "heritability" is a proportion, not an absolute quantity. In populations of subjects who are developing a disease like AD "ahead of schedule", it is likely that there is substantial environmental provocation to account for the acceleration of onset. Given a constant degree of genetic input, heritability will then be lower. These observations suggest that the premise that an earlier onset of AMD is more likely to be genetic than a form of AMD with a more typical age of onset may be invalid [34].

The Beaver Dam population provided strong evidence for a major gene locus for AMD [23]. A later study by Seddon et al [26] evaluated first degree relatives of 119 AMD cases and first degree relatives of 72 control individuals without AMD. The majority of the relatives were siblings, though living parents and children over age 40 were also included. The prevalence of AMD was significantly higher among first-degree relatives of AMD case probands (23.7%) compared with that observed for first-degree relatives of control probands (11.6%). The overall age- and sex-adjusted odds ratio was 2.4 (95% CI: 1.2-4.7), p=0.13. For the subset of cases with choroidal neovascular membranes, the odds ratio was 3.1 (95% CI:1.5-6.7). Dr. Klaver and Dr. de Jong conducted a similar study using 101 cases with end-stage AMD and 154 randomly selected subjects without evidence of AMD. They found that the siblings of cases had an odds ratio of early AMD of 4.8 (95% CI 1.8-12.2) and an odds ratio for end-stage AMD of 19.8 (95% CI 3.1-126). The children of cases had an odds ratio of 6.6 (95% CI 1.4-31.8) for early AMD changes. Not surprisingly, none of the children of AMD cases were found to have endstage AMD. Overall, they attributed the occurrence of the disease to a genetic component for 76% of the subjects with a family history of AMD and that 23% of all of the end-stage AMD could be due to a genetic basis. [25]

Recently apolipoprotein E has been shown to be associated with AMD based upon the reduced prevalence of the ε4

allele in patients with exudative AMD as compared to a control sample [35]. Klaver et al [36] have reported similar findings as well as evidence of the ApoE protein within AMD-associated deposits in the macula. This association may be the exact opposite of the situation in AD in which the genotype at the polymorphic locus APOE (which encodes the protein apolipoprotein E) strongly predicts the age at which susceptible individuals will develop AD [37-39]. In particular, the ε4 allele (one of three normal variants) appears to accelerate the onset of AD. This acceleration results in higher age-specific prevalence and incidence of AD in those who have an ε4 allele, and especially in ε4 homozygotes. Thus, in epidemiologic studies, the ε4 allele of APOE initially appeared as a deterministic factor for AD, though now the consensus is that it is a modifying gene. It is important to note that the relationship of APOE to AD was established by nonparametric linkage analysis, thus showing that this approach can successfully identify causative as well as modifier genes related to a complex genetic disorder.

What is the relationship of other hereditary macular dystrophies with AMD?

Studies of the tissue inhibitor of metalloproteinase-3 (TIMP-3) which has been implicated in Sorsby's fundus dystrophy have failed to indicate an association with AMD [40]. Similarly, peripherin mutations are well-described to cause macular dystrophies in a number of families [15,18,41], but constitute a very small percentage of AMD cases. The recent mapping of the genetic loci for malattia leventinese [42], North Carolina macular dystrophy [43], and several moderately-sized AMD families [44; unpublished data] provide additional opportunities to investigate these regions of the genome for candidate genes and their broader relationship with common forms of AMD. As discussed in another session of this symposium, the role of the ABCR gene associated with Stargardt's disease with AMD has been proposed [12] and contested [45].

While many investigators have looked upon the hereditary macular dystrophies as specific models of AMD, it is more likely that they represent fairly rare genetic events along a common pathway that leads to retinal/RPE degeneration. Again, Alzheimer's disease has proven to be a useful paradigm for understanding the relationship of rare familial forms of senile dementia with AD. The cloning of the gene for the β-amyloid precursor protein (APP) and the eventual identification of disease-producing mutations in APP proved that AD could be provoked by genes. Furthermore, since all those with functional mutations in these genes eventually developed AD, it was clear that genes could be sufficient, as well as necessary to provoke the AD phenotype. Later discoveries of other rare mutations on other chromosomes made it clear that the AD phenotype was a "final common pathway" that could be provoked by several different genes. The relevance of β-amyloid to AD pathogenesis has emphasized that each of these mutations alters β-amyloid's metabolism in some way. Clearly the investigation of monogenic macular dystrophies will play a key role in the study of AMD, although it will take coordinated effort with other approaches to establish the extent to which they account for the common forms of AMD.

How does one explore AMD as a complex genetic disorder?

In complex, age-dependent disorders, genes can act (either alone or in concert with environmental factors) in any of several ways. It is important to examine population data that can clarify whether genes are effect modifiers or fundamental susceptibility factors. Those who would "go for the gold" in seeking to explain disease susceptibility or pathogenesis may wish to investigate the latter.

In order to test candidate genes and genetic loci associated with classical macular dystrophies as well as search for any genetic loci that may contribute to AMD susceptibility, several groups are relying upon the use of nonparametric linkage studies using large numbers of relatively small AMD families (two or more affected individuals, generally siblings). The nonparametric approach allows the investigation of the potential of association of a genetic locus with AMD without specifying a model of inheritance (dominant or recessive) and without confoundment by genetic heterogeneity. The concept is relatively simple. If two members (for example, siblings or cousins) both have AMD, then it is likely that the genes that contribute to AMD susceptibility are among those shared by those individuals. If we examine many such families, the shared regions that specifically contribute to AMD will be preferentially observed, rising above random chance. With a sufficient number of families, even a relatively minor genetic locus that contributes to AMD (either in a small percentage of families or because it exerts a relatively minor influence) can be observed. The number of families that must be analyzed is determined by the complexity of the genetics of the condition itself. While we can do simulations to predict the ability to detect linkage of AMD with a major locus [6,46], we don't really know how many families have to be studied until the statistical tests for linkage are evaluated.

In theory, even if many genes play a role in AMD, the contribution of a specific locus can be assessed if one evaluates a sufficient number of families. If a locus contains a gene that contributes to only a small percentage of AMD cases, it can be easily overlooked unless one analyzes an enormous number of families. An example of this issue can be seen in Dr. Stone's efforts to detect linkage of the GLCA1 locus with adult open angle glaucoma. Nonparametric analyses of his glaucoma families failed to detect linkage with this locus and yet he has convincingly shown that mutations in the GLCA1-related gene are responsible for approximately 4% of open angle glaucoma cases [47; personal communication, Edwin Stone, 5 August 1998].

Gorin et al. conducted a 20 cM autosomal, genome-wide scan for AMD susceptibility genes using 120 AMD families. The diagnosis of AMD was made by a combination of photographs and eyecare records with a grading system that assessed the severity of macular alterations and the likelihood that the underlying condition is AMD versus other causes of macular degeneration. Because of the method of ascertainment primarily from ophthalmology and vitreoretinal practices, approximately 65% of the patients had choroidal neovascular membranes as a feature of their disorder. No evidence of linkage to any of the known macular or retinal dystrophy loci was found,

suggesting that no single hereditary macular dystrophy appears to be responsible for a major proportion of AMD cases. Despite the initial identification of several AMD susceptibility loci from the first genome-wide scan and a second,10 cM genome-wide scan using 240 families, confirmatory analyses with additional families and markers have failed to support strong evidence for linkage at a single locus. Thus, this approach, while continuing to offer the promise of identifying AMD-related loci, has not yet produced results. This may be a reflection of the genetic heterogeneity of this group of disorders in which any given gene contributes to less than 5-10% of the familial AMD population. This limitation may eventually be overcome by evaluating many more families or working with populations with less genetic diversity.

What is the role of environmental factors if AMD is a complex genetic disorder?

It is a common misperception, that a condition that has a strong genetic basis must occur independently of environmental factors. Genetic susceptibility is frequently confused with genetic determinism. For example, there is epidemiologic evidence that smoking is a significant risk factor for AMD [48-52] and other dietary factors have been implicated [53,54]. Again, Alzheimer's disease offers a opportunity to consider environmental factors that may modify the age of onset or likelihood of developing disease. At least four environmental influences (smoking, use of nonsteroidal anti-inflammatory medications, hormone replacement therapy, and antioxidant vitamins) may modify the genetically determined risk for AD. Among the most dramatic demonstration of these effects have been studies conducted in identical twin pairs or siblings [31]. Here, the control on genes offers obvious advantages in the "case-control" design, since such studies largely avoid confounding with genes. They also allow for studies of environmental factors that act specifically to modify onset (not otherwise to alter risk).

The co-twin control and sib designs offer substantial promise for the discovery of risk factors for AMD and other complex disorders [55]. Once relevant genes are discovered, one can conduct incidence (or even careful prevalence) studies that show the influence of these genes at the population level. As more genes are identified, there is the possibility of correlating specific phenotypes (clinical features, age of onset, likelihood of progression to either atrophy or choroidal neovascular membranes) with underlying genetic variants. In AD, it now seems that APOE polymorphism influences the onset of AD, but does not otherwise influence susceptibility. [39] A number of authors have (mistakenly, in our opinion) characterized APOE as a "major susceptibility locus for AD". In fact, APOE influences onset, and thus age-specific risk, but not susceptibility in the most specific sense of the word.

Functional genomic approaches to AMD

Functional genomics is a relatively new term that describes the evaluation of changes in transcript expression in one or more specific cells or tissues in relation to an underlying alteration in biology. That alteration may be the result of transformation of a cell type to a malignancy, the response to a pharmacologic agent, alterations in cell expression during development, or the response of a tissue to a genetic alteration such as seen in a genetic disorder, gene manipulation or infection. New technologies such as cDNA arrays on glass slides [56], oligonucleotide arrays on chips [57,58], serial analysis of gene expression (SAGE) [59-61] and differential display [62,63] offer new opportunities to investigate the cellular and tissue responses to AMD. Rather than relying on the linkage of one or more genomic regions with AMD in single or multiple families, this approach focuses on patterns of transcript expression in normal and AMD affected tissues to determine the cascade of molecular events involved in various stages and phenotypes of AMD. Some of these methods employ arrays of known transcripts (such as the cDNA and oligonucleotide arrays), while other approaches (such as SAGE and differential display) provide the capability to discover new genes within the retina, pigment epithelium, and choroid. Kuehn and Hageman have applied differential display [64] and gene arrays to identify a variety of differentially expressed molecules in the RPE derived from donors with AMD as compared to the expression patterns observed in the RPE from healthy eyes [unpublished data].

Such strategies offer the potential of expanding the set of genes that are involved in the pathogenesis of AMD as well as the normal function of the retina and RPE/choroidal interface, but they cannot by themselves establish causality. As alluded to above, it is likely that AMD represents a common pathway of degeneration, much like that proposed for Alzheimer's disease. Such studies can establish the interrelationship of the different genes and proteins that contribute to this pathway, so that as one or more genes for AMD are identified, we can begin to assemble the complex pieces that comprise the puzzle of AMD pathogenesis. In combination with other genetic approaches, functional genomic methods offer an invaluable tool for eventually understanding the interactions of the many cellular processes that maintain the eye and contribute to AMD.

Conclusions

The elucidation of the genetic bases of AMD is one of the great challenges of ophthalmic research within the next decade. The combination of multiple genetic approaches offers the best opportunity to establish the role of one or more genes in the pathogenesis of this disorder. The goals are: to achieve the means of identifying individuals who have an increased risk for developing AMD before they are symptomatic or have serious pathology, to understand the pathogenesis of AMD at a molecular level so that new therapies can be developed and tested, and to offer a therapeutic approach that combines environmental, dietary and pharmacologic modalities that will minimize the impact of genetic susceptibility and preserve sight.

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