

Review article

Genetic susceptibility to age related macular degeneration

John R W Yates, Anthony T Moore

Abstract

Age related macular degeneration (AMD) is the leading cause of visual impairment in the elderly and a major cause of blindness in the developed world. The disease can take two forms, geographic atrophy and choroidal neovascularisation. The pathogenesis of AMD is poorly understood. There are undoubtedly environmental and other risk factors involved and the adverse effect of smoking is well established. Several studies have shown that genetic factors are important but leave uncertainty about the magnitude and nature of the genetic component and whether it varies with the type of AMD. Several hereditary retinal dystrophies show similarities to AMD and these genes are potential candidate susceptibility genes. Particular interest has focused on the *ABCR* gene which is responsible for autosomal recessive Stargardt macular dystrophy. It has been claimed that heterozygotes for *ABCR* mutations are predisposed to AMD but the data are conflicting. Studies of the genes responsible for autosomal dominant Sorsby fundus dystrophy, Doyme honeycomb retinal dystrophy, and Best disease have given negative results. In one large AMD family, linkage has been reported to markers in 1q25-q31. Recent data suggest that the ApoE ϵ 4 allele may be associated with reduced risk of AMD. A better understanding of the genetic factors in AMD would contribute to understanding the pathogenesis. If those at risk could be identified it may be possible to modify lifestyle or develop novel therapies in the presymptomatic stage to prevent disease or decrease its severity.

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Age related macular degeneration (AMD) is the leading cause of visual impairment in the elderly and the commonest cause of blindness in the developed world. As such, it represents a major public health problem. Genetic factors are important and the available data suggest

that AMD may well be caused by environmental factors triggering disease in genetically susceptible subjects. Several hereditary retinal dystrophies have phenotypic similarities to AMD and the genes responsible for these conditions are potential candidate susceptibility genes. Recent interest has focused on the gene for Stargardt macular dystrophy and the claim that heterozygotes are predisposed to AMD. Here we review what is known about the genetics of AMD and possible susceptibility genes.

Disease phenotype

Degenerative changes in the macular area of the retina are an increasingly common finding from 50 years of age onwards. The characteristic ophthalmoscopic lesions of age related maculopathy (ARM) are discrete whitish-yellow spots called drusen (particularly the type called soft drusen, fig 1) and areas of increased pigmentation or retinal pigment epithelium (RPE) atrophy. If these are the only lesions present, the condition is best referred to as early ARM, reserving the terms late ARM or age related macular degeneration (AMD, senile macular degeneration) to describe more advanced changes which are likely to be associated with visual impairment. Two manifestations of AMD can be distinguished, geographic atrophy (GA, also referred to as atrophic, non-exudative, or dry AMD, fig 2) and choroidal neovascularisation (CNV, also referred to as neovascular, exudative, wet, or disciform AMD, fig 3). GA is characterised by extensive atrophy of the retinal pigment epithelium and overlying photoreceptor cells (typically defined as one or more areas at least 175 μ m in diameter). CNV is characterised by aberrant choroidal angiogenesis. The new vessels are fragile and often bleed leading to the formation of fibrovascular scars and irreversible visual loss. CNV is responsible for the majority of cases of severe loss of central vision. This is often of sudden onset with devastating psychological and practical consequences. The classification and grading of ARM and AMD is complicated by the great variation in number, location, size, and types of lesion that occurs. Over the years, a variety of definitions have been used in epidemiological studies which makes comparison difficult. In the hope of pro-

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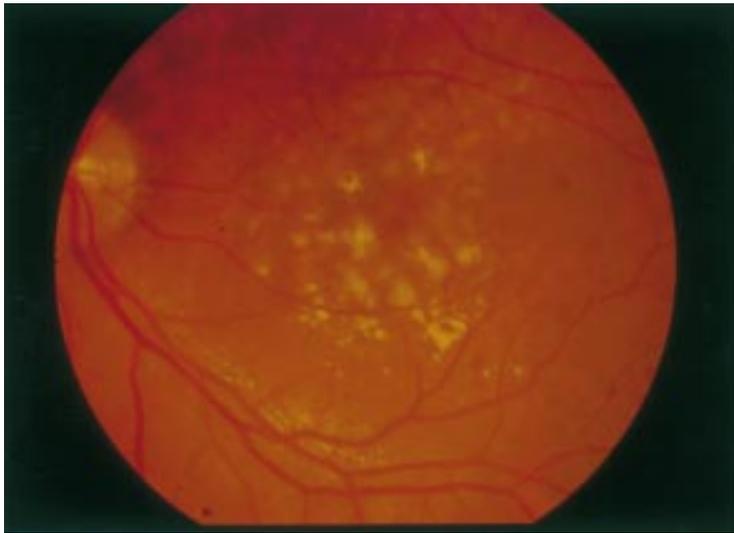


Figure 1 Multiple large soft drusen in the left macular region typical of age related maculopathy.

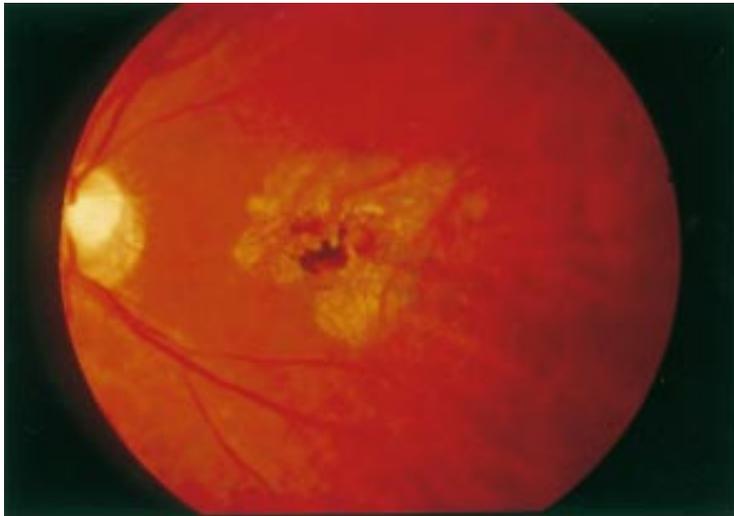


Figure 2 Geographic atrophy involving the left macular region.

moting uniformity, a classification and grading system for ARM and AMD based on the detailed assessment of colour fundus photographs has been proposed by The International Age-related Maculopathy Epidemiological Study Group.¹

Burden of disease

AMD accounts for approximately 50% of all cases of registered blindness and partial sight in England and Wales.² Moreover, the prevalence of AMD appears to be rising.³ At the same time, demographic change means that the population of at risk subjects is increasing.

Numerous population studies have shown that the frequency of ARM/AMD begins to rise from around 50 years of age. The Beaver Dam Eye Study⁴ provides representative prevalence figures: in the age group 65-74 years, early ARM was present in 18.0% and late ARM (AMD) in 1.4%; for patients over 75 years, the corresponding figures were 29.7% and 7.1%. For the early changes of ARM, frequencies were similar in males and females. In patients

over 75, late ARM (AMD) was commoner in females (7.8%) than males (5.6%).

Options for the treatment of AMD are limited. For GA, low vision aids are all that can be offered. For CNV the mainstay of therapy is laser photocoagulation, but only a minority of patients are suitable for treatment and recurrence is common.

Pathogenesis

The pathogenesis of ARM/AMD is poorly understood and this hampers the development of rational therapies. In the normal eye throughout life there is a regular turnover of the photoreceptor outer segments which contain the photosensitive visual pigments. Material shed from the outer segments is engulfed and digested by the underlying retinal pigment epithelium (RPE) and ultimately cleared by the capillaries of the choroid (the choriocapillaris). The RPE is separated from the choriocapillaris by a multilayered structure called Bruch membrane. It is known that this membrane thickens with age and that in the early stages of ARM/AMD there is accumulation of debris in the membrane which contributes to the development of drusen, one of the characteristic clinical features of early ARM. It is likely that this debris is derived from the cytoplasmic material being continually discharged into the inner portion of Bruch membrane from the RPE.

It is not known why material accumulates in Bruch membrane, why some patients are more susceptible than others, and what determines the subsequent progression to GA, detachment of the RPE, or CNV. Bird⁵ has suggested that genetic and other factors predisposing to the development of ARM/AMD might exert their effect by (1) increasing outer segment turnover, (2) reducing activity of RPE degradative enzymes, (3) causing free radical damage to the substrate of degradation, (4) modifying the processes of ageing in Bruch membrane such as the cross linkage of collagen, or (5) reducing the clearance of material from Bruch membrane.

Risk factors

There are undoubtedly environmental and other risk factors that contribute to ARM/AMD. The adverse effect of smoking is well established.⁶⁻⁸ Other possible risk factors include hypertension,⁹ raised plasma fibrinogen levels,⁸ blue iris colour,¹⁰ poor skin tanning or abnormal skin sensitivity to sunlight,^{10 11} and lightening of iris colour with age.¹² Dietary antioxidants such as carotenoids¹³ and zinc¹⁴ may be protective but the evidence is not conclusive and further studies are needed.¹⁵ Moderate wine consumption may also be protective.¹⁶ The prevalence of AMD varies between racial groups, tending to be lower in non-white populations.^{17 18} In the Japanese, AMD was said to be virtually unknown 30 years ago. This was thought to have a genetic basis, but it now seems more likely to be because of environmental factors, since the prevalence has apparently increased dramatically in urban communities over recent years.¹⁹



Figure 3 (Above) Subretinal haemorrhage and fluid secondary to choroidal neovascularisation involving the left macular region. (Below) Appearance 12 months later showing extensive scarring.



In a UK study of Asians and Europeans living in the same city, no difference in the prevalence of AMD was observed.²⁰ The Inuit of Greenland appear to have a particularly high incidence of AMD,²¹ but it is not known whether this has an environmental or genetic basis.

Genetic epidemiology

For a condition as common as AMD, there have been relatively few studies of the genetic epidemiology, although from the available data it is clear that genetic factors are important. The familial nature of AMD has long been recognised.²² Klein *et al*²³ reported eight of nine monozygotic (MZ) twins concordant for AMD. Meyers *et al*²⁴ reported 100% concordance in 25 MZ twins compared to 42% concordance in 12 dizygotic (DZ) twins. Gottfredsdottir *et al*²⁵ found 90% concordance in 50 MZ twins which was significantly higher than for twin/spouse pairs. Further evidence of a genetic predisposition to ARM was provided by Pigué *et al*,²⁶ who compared the characteristics of drusen in spouses and sibs of AMD

patients and found a marked concordance between sibs but not with spouses. Smith *et al*⁶ have confirmed in a questionnaire study that family history is a risk factor, obtaining an odds ratio of 4.2. Two studies from the United States have investigated the frequency of AMD in the sibs of index cases and controls. Hyman *et al*²⁷ found that 29/146 (20%) of the sibs of index cases were affected, compared to 12/152 (8%) of the sibs of controls, giving an odds ratio of 2.9. In the study by Seddon *et al*²⁸ the corresponding figures were 35/98 (36%) for cases and 15/112 (13%) for controls, giving an odds ratio of 2.7. However, the limitation of both studies was that the disease status of sibs was dependent on data provided by their ophthalmologist or optometrist²⁷ or extracted from their medical records²⁸ rather than being based on assessment of fundus photographs.¹ In a similar case-control study from Belfast, fundus photographs were obtained in half of the sibs but diagnosis in the rest relied on reports from ophthalmologists or opticians²⁹: 20/81 (25%) sibs of index cases were affected but only 1/78 (1%) sibs of controls, giving a relative risk of 19. Klaver *et al*³⁰ studied fundus photographs of first degree relatives of 87 index cases with late AMD and 135 controls and obtained a relative risk of 4.2. There was evidence that relatives expressed features of ARM at a younger age “suggesting that genetic susceptibility may play an important role in determining the onset of disease”. One large population based study has provided data on genetic factors for ARM/AMD based on graded fundus photographs of 1285 subjects from 564 sibships. Using the resulting scores for segregation analysis, Heiba *et al*³¹ concluded that the number of genes predisposing to AMD was small and there may be a single locus acting as the major determinant. Taken together, these studies leave some uncertainty about the magnitude and nature of the genetic component in AMD and whether it varies with type of AMD or with age at onset. Interestingly, in the study by Seddon *et al*,²⁸ for exudative AMD the odds ratio was 3.1 whereas for GA the odds ratio was only 1.5 and not statistically significant. The authors concluded that “the data suggest that AMD may be a heterogeneous condition” and “for geographic atrophy and exudative disease...there may be different relative contributions of genetic and environmental factors to the origin of these subtypes”.

Candidate genes

Several hereditary retinal dystrophies have some phenotypic similarity to AMD. Stargardt disease and Best macular dystrophy commonly result in macular atrophy, while drusen are a prominent feature of Doyme honeycomb retinal dystrophy (autosomal dominant radial drusen, Malattia Leventinese) followed later by the development of CNV, which is also a common feature of Sorsby fundus dystrophy. The genes responsible for these conditions are attractive candidate susceptibility genes for AMD.

Stargardt disease (STGD1) is the commonest of the autosomal recessive macular dystrophies. It is characterised by juvenile or early

adult onset and leads to progressive atrophy of the macular RPE and overlying photoreceptors. The condition is caused by mutations in the *ABCR* gene (a member of the ATP binding cassette transporter superfamily).³² *ABCR* corresponds to a previously identified rod outer segment protein called rim protein (RmP). Allikmets *et al*³³ screened unrelated AMD patients for mutations in the 51 exons of the *ABCR* gene by heteroduplex analysis (HA) and single strand conformational polymorphism analysis (SSCP) followed by sequencing. From these data, 13 different sequence changes, mostly missense mutations, present in 26/167 (16%) of AMD patients, were deemed to be associated with AMD on the grounds that they were not observed or were significantly less frequent in controls. The authors concluded that *ABCR* is an important susceptibility gene for AMD. Critics have questioned this interpretation of the data and the justification for removing from consideration sequence variations that occurred at appreciable frequency in controls.^{34 35} With inclusion of these variants it is arguable whether there was a significant difference between AMD cases and controls.³⁴⁻³⁶ Moreover, it has been pointed out that the correct experiment in the controls should have been HA/SSCP mutation screening as in the cases, the implication being that the controls would also show a variety of rare polymorphisms, different from those found in the cases but at a similar frequency.^{34 35} In the subsequent study by Stone *et al*,³⁷ 182 AMD cases and 96 controls were completely and equally screened, showing a large number of sequence variations in both groups, but no significant differences between them. Other studies have given negative results.^{38 39} Meanwhile, Allikmets *et al*³⁶ have reported additional data in support of their original findings, including studies of Stargardt disease families where relatives with AMD have been shown to be *ABCR* mutation carriers.^{40 41} It remains to be seen how this controversy will be resolved but the available evidence does not yet establish a significant role for *ABCR* in determining susceptibility to AMD.

Doyme honeycomb retinal dystrophy (DHRD) (*syn* dominantly inherited radial drusen or Malattia Leventinese) is an autosomal dominant disorder characterised by the appearance of drusen in early adult life. The locus maps to 2p16-2p21.⁴²⁻⁴⁴ Using six markers spanning this region to study 51 affected sib pairs from 28 multiplex AMD families, De La Paz *et al*⁴⁵ reported preliminary evidence suggestive of linkage. Recently, the *DHRD* gene was identified.⁴⁶ In all 39 DHRD families studied, affected subjects had a single non-conservative mutation Arg345Trp in a gene designated *EFEMP1* (for EGF containing fibrillin-like extracellular matrix protein 1) encoding a protein homologous to a family of extracellular matrix glycoproteins known as fibulins. None of a panel of 494 patients with AMD carried this mutation and no abnormalities were found in these patients on screening the entire *EFEMP1* coding region by SSCP.⁴⁶

Best disease (*syn* vitelliform macular dystrophy type 2) is an autosomal dominant macular dystrophy mapping to 11q13. The gene was recently isolated^{47 48} and there is one study providing evidence that mutations in the bestrophin gene do not play a significant role in predisposition to AMD.⁴⁹ Sorsby fundus dystrophy is an autosomal dominant disorder caused by mutations in the tissue inhibitor of metalloproteinases-3 gene (*TIMP-3*),⁵⁰ which plays a central role in extracellular matrix modelling. Investigations of *TIMP-3* as a predisposing gene for AMD by linkage analysis, sib pair analysis, association studies, and mutation screening have given negative results.^{51 52} Mutations in the *peripherin/RDS* gene can give rise to a variety of retinal phenotypes including a macular dystrophy with some resemblance to AMD,⁵³ but mutational analysis in 50 AMD patients did not identify any significant sequence changes.⁵⁴ In a large AMD family with 10 affected members, Klein *et al*⁵⁵ have reported linkage to markers at 1q25-q31. Finally, Klaver *et al*⁵⁶ recently reported that the ApoE ϵ 4 allele is associated with reduced risk of AMD (odds ratio 0.43) and the ϵ 2 allele with a slightly increased risk (odds ratio 1.5). They also provided preliminary evidence that ApoE may have some involvement in the pathogenesis of AMD by showing ApoE immunoreactivity in AMD associated drusen and basal laminar deposits. This merits further investigation.

Need to understand the genetic component of AMD

From the available data, it appears that AMD is caused by environmental factors triggering disease in genetically susceptible subjects. Identifying the genetic factors would contribute to understanding the pathogenesis. If those at risk could be identified it may be possible to modify lifestyle or develop novel therapies in the presymptomatic stage to prevent disease or decrease severity. The high prevalence of the disease in the western population and the apparent rise in prevalence in racial groups not previously considered to be at risk highlights the need for more research on the pathogenesis of AMD.

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