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Age-related Macular Degeneration

Second Edition

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Preface to the Second Edition

The diagnosis of age-related macular degeneration (AMD), particularly the exudative form, was dreaded by patients and doctors alike. This nearly always meant blindness for the patient as the doctor was helpless to intervene. Laser photocoagulation was an important development in therapy, but that treatment helped only a small minority of affected patients. Fortunately recent landmark developments in several interrelated fields have changed the outlook for patients with exudative AMD. Many patients now have visual acuity improvement or stabilization. There are still daunting tasks ahead however. Demographic trends and higher life expectancy mean the condition will become more prevalent in years to come. There are other aspects of AMD that threaten visual function and these are the subject of intensive research.

Knowledge of the subject has increased considerably since the first edition of this book. This has been primarily due to the intensification of broad-based, multidisciplinary research. Not only new methodological tools from areas such as molecular and cell biology, biochemistry, and molecular genetics have contributed to this status, but also further developments in the area of imaging and pharmacology. We are therefore optimistic that therapies for an ever increasing number of AMD patients will become available as a result of current and future developments in treatment.

The chapters in the 2nd edition have been fundamentally revised and relevant new developments and findings considered. In the field of pathogenetic factors a chapter has now been devoted to the role of the complement system in multifactorial, complex AMD. Furthermore, the role of imaging procedures including spectral-domain optical coherence tomography and fundus autofluorescence is addressed in detail. New therapeutic approaches based on deep insights into the underlying molecular mechanisms are examined both with respect to neovascular and progressive dry AMD.

A main objective of the book is to summarize clearly and understandably the current level of knowledge of pathogenesis, diagnostics and therapy of AMD and to point to the possibilities and limits presented by the therapeutic approaches. The bibliography is necessarily a selection from the considerably large number of publications of recent years.

We would like to thank the outstanding scientists and clinicians who have contributed their expertise to the various chapters. Our thanks also extend to our mentors, colleagues, patients and students for their diverse scientific and clinical suggestions. We thank the staff at the publishing company Springer for their professional and punctual realization of the book in the fast moving and expanding field of AMD.

Bonn, 2012 — Frank G. Holz
Münster, 2012 — Daniel Pauleikhoff
New York, 2012 — Richard F. Spaide
London, 2012 — Alan C. Bird

Contents

Part IV Prophylaxis and Therapy

List of Abbreviations

ABCA1	ATP-binding cassette, subfamily A
AD	Alzheimer's disease
AGE	Advanced glycation end products
ALA	Alpha linoleic acid
AMD	Age-related macular degeneration
APC	Alternative pathway of complement
APOE	Apolipoprotein E
ARM	Age-related maculopathy
ARMS2	Age-related maculopathy susceptibility 2
BCEA	Bivariate contour ellipse calculated area
BCVA	Best corrected visual acuity
BLD	Basal laminar deposits
BM	Bruch's membrane
BMI	Body mass index
CC	Choriocapillaris
CCD	Charge-coupled device
CCTV	Closed circuit television system
CDCV	Common disease – common variant
CDRV	Common disease – rare variant
CEP	Carboxyethylpyrrole
CETP	Cholesteryl ester transfer protein
CFB	Complement factor B
CFH	Complement factor H
CFI	Complement factor I
CI	Confidence interval
CME	Cystoid macular edema
CNP	Copy number polymorphism
CNTF	Ciliary neutrophic factor
CNV	Choroidal neovascularization
CR1	Complement receptor 1
CRP	C-reactive protein
CRT	Central retinal thickness
CSC	Central serous chorioretionopathy
cSLO	Confocal scanning laser ophthalmoscope
DA	Disc area
DAF	Decay-accelerating factor
DHA	Docosahexaenoic acid
ECM	Extracellular matrix

EDI-OCT	Enhanced depth imaging spectral-domain optical coherence tomography
EOG	Electro-oculogram
EPA	Eicosapentanoic acid
ESR	Erythrocyte sedimentation rate
F1	Factor 1
FAF	Fundus autofluorescence
FAZ	Foveolar avascular zone
FDA	Food and Drug Administration
FP	Fundus perimetry
FVPED	Fibrovascular pigment epithelial detachment
GA	Geographic atrophy
GCL	Ganglion cell layer
GWAS	Genome-wide association study
HDL-c	High-density lipoprotein cholesterol
HTRA1	High temperature requirement factor A1
ICG	Indocyanine green
ICAM	Intracellular adhesion molecules
IL6	Interleukin 6
IOP	Intraocular pressure
IPE	Iris pigment epithelium
IR	Infrared
IV	Inverse variance
IVB	Intravitreal bevacizumab
IVR	Intravitreal ranibizumab
IVTA	Intravitreal triamcinolone
LCPUFA	Long-chain polyunsaturated fatty acids
LDC	Linkage disequilibrium
LDL	Low density lipoprotein
LF	Lipofuscin
LIPC	Lipase C
LLUS	Late leakage of undetermined source
logMAR	Logarithm of the minimum angle of resolution
LPL	Lipoprotein lipase
LSC	Long spaced collagen
LVA	Low vision aid
MAC	Membrane attack complex
MAF	Minor allele frequency
MBL	Mannose-binding lectin
MCP	Membrane cofactor protein
MHC	Major histocompatibility complex
MMP	Matrix metalloproteinase
MPGN	Membranoproliferative glomerulonephritis
MPOD	Macular pigment optical density
NV-AMD	Neovascular age-related macular degeneration
OCT	Optical coherence tomography
OR	Odds ratio
ORCA	Occult retinal choroidal anastomosis

PAMP	Pathogen-associated molecular pattern
PAR	Population attributable risk
PATCH	Pigment epithelium-choroid-translocation
PCV	Polypoid choroidal vasculopathy
PD	Pupillary distance
PDGF	Platelet-derived growth factor
PDT	Photodynamic therapy
PE	Pigment epithelium
PED	Pigment epithelium detachment
PEDF	Pigment epithelium derived factor
PFCL	Perfluorocarbon liquid
PHP	Preferential hyperacuity perimeter
PLGF	Placental growth factor
PLEKHA1	Pleckstrin homology domain-containing protein family A member 1
PNH	Paroxysmal nocturnal hemoglobinuria
PON1	Paraoxonase 1 gene
POS	Photoreceptor outer segment
PRL	Preferred retinal locus
PRN	Pro re nata
PRR	Pattern recognition receptor
PSDDS	Posterior segment drug delivery system
PVR	Proliferative vitreoretinopathy
RAP	Retinal angiomatous proliferation
RBP	Retinol-binding protein
RCA	Regulators of complement activation
RCOphth	Royal College of Ophthalmologists
RCT	Randomized controlled trial
RF	Reduced fluence rate
RNFL	Retinal nerve fiber layer
ROS	Reactive oxygen species
RPE	Retinal pigment epithelium
RR	Relative risk
RTK	Receptor tyrosine kinases
rTPA	Recombinant tissue plasminogen activator
RVAC	Retinal vascular anomalous complexes
SD-OCT	Spectral domain optical coherence tomography
SF	Standard fluence rate
SLD	Superluminescent diodes
SLO	Scanning laser ophthalmoscope
SNP	Single nucleotide polymorphism
SOD2	Superoxide Dismutase 2
Sr-90	Strontium-90
SS-OCT	Swept source optical coherence tomography
TD-OCT	Time domain optical coherence tomography
TIMP	Tissue inhibitor of metalloproteinases
TLR	Toll-like receptor
TP-H	TEMPOL-H

UTR	Untranslated region
VA	Visual acuity
VCM	Visual cycle modulators
VEGF	Vascular endothelial growth factor
VPDT	Verteporfin photodynamic therapy
WWC	White cell count

Part I

Pathophysiology

Epidemiology of AMD

1

L. Ho, R. van Leeuwen, P.T.V.M. de Jong,
J.R. Vingerling, and C.C.W. Klaver

Core Messages

- Tremendous progress has been made in the identification of associated genes. The major susceptibility genes are *CFH* and *ARMS2/HTRA1*, which are involved in over 60% of severely affected cases. This underscores the pivotal role of the inflammation and oxidative stress pathways in the pathogenesis of AMD. Established genetic risk markers with smaller effect are the *C3*, *C2/FB*, *CFI*, and *APOE* genes. Genome-wide association studies reported associations with *TIMP3*, *LIPC*, *CETP*, *LPL*, and *ABCA1*, suggesting that lipid metabolism plays a role in AMD pathogenesis.
- All ethnicities showed a strong increase in AMD frequency with age. The frequency of late AMD was highest in Caucasians, followed by Asians and Hispanics, and lowest in Africans. Africans also had the lowest frequency of early AMD.
- Soft drusen and pigmentary abnormalities are the most significant fundus features which increase the risk of AMD. After one eye develops late AMD, the 5-year risk estimates of second eye involvement were between 30% and 40%.
- Smoking is the most consistent and most important environmental risk factor. Prominent protective factors are antioxidants, zinc, and omega-3 fatty acids. Less conclusive but suggestive risk factors are BMI, cataract surgery, and systemic hypertension.
- Interactions between genes and environmental factors are likely. Reports suggest that the *CFH* gene may interact with smoking; CRP level; erythrocyte sedimentation rate; BMI; and intake of antioxidants, zinc, and omega-3 fatty acids. *LOC387715* appears to interact with smoking, CRP, IL-6, sICAM-1, and PAI-1. The *APOE* genotypes may modify the smoking-associated risk of AMD.

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1.1 Introduction

This chapter will provide an update on the epidemiology of age-related macular degeneration (AMD) as it has developed during the past few years, since the last

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Table 1.1 Classification of age-related macular degeneration in epidemiologic studies

Detection	Grading of color fundus transparencies using a macular grid centered on the fovea with a diameter of 6,000 μm
Overall term	Age-related macular degeneration
Exclusion	Other diseases must be excluded; e.g. ocular trauma, retinal detachment, high myopia, chorioretinal inflammation or infection
Early age-related macular degeneration	Soft indistinct or reticular drusen; any soft drusen type with RPE depigmentation or with increased retinal pigment
Late age-related macular degeneration	Atrophic or neovascular macular degeneration
– Atrophic AMD = geographic atrophy	Any sharply delineated lesion >175 μm in diameter with apparent absence of the RPE in which choroidal vessels are more visible than in the surrounding areas.
– Neovascular AMD = exudative AMD	RPE detachment associated with other signs of AMD; subretinal or sub-RPE neovascular membranes; scar, glial or fibrin-like deposits, subretinal hemorrhages, or hard exudates not related to other diseases.

edition in 2003. We shall review the current epidemiological literature, and discuss diagnosis, frequency, genetic and environmental factors, and the possible interaction between them.

1.2 Classification

In 1995, investigators of various epidemiologic studies agreed on a uniform classification of age-related maculopathy on color photographs of the macula lutea without implication of visual acuity [1]. The classification of this international agreement is summarized in Table 1.1. For the purpose of this review, we will maintain the terminology of this international system.

1.3 Frequency

1.3.1 Prevalence

Population-based studies on the prevalence of early and late AMD have been conducted in various parts of the world as shown in Fig. 1.1. Herein we included only those population-based studies that used the standardized grading systems [1, 2]. Estimates for both early and late AMD show a strong increase with advancing age in all studies, although there was marked variation in the reported prevalence estimates. Population estimates varied more for early AMD than for late AMD. This variation may be genuine to some extent, but differences in classification of drusen size and type will account for some of the dissimilarities. By contrast, there is close agreement on grading of geographic atrophy and subretinal neovascularization; therefore, the differences among studies are more likely to be genuine.

Figure 1.2 shows a comparison of prevalence data for early and late AMD for persons from African, Asian, Caucasian, or Hispanic descent based on data reported in the population-based studies. Prevalence rates for early AMD were positively correlated with age across all races/ethnicities. This was most pronounced for Caucasians and Hispanics and to a somewhat lesser extent for Asians and Africans. For persons under 75 years of age, Hispanics appeared to have higher frequencies of early AMD compared with the other races/ethnicities. Over the age of 75 years, the frequency of early AMD for Caucasians exceeded that of the other races/ethnicities. Across all age strata, Africans had the lowest frequency of early AMD, followed by Asians. A reasonable overall prevalence for early AMD among Caucasians, Hispanics, Asians, and Africans aged under 55 years was 4%, 6%, 3%, and 3%, respectively. These prevalences increased to 24%, 22%, 13%, and 11% for persons aged 75 years and older. With respect to the frequencies of late AMD, there was an exponential age-related increase in Caucasians, a strong increase in Asians, a moderate increase in Hispanics, and a slight increase in Africans.

A reasonable overall prevalence for late AMD for persons aged under 55 years ranged between 0.0% and 0.2% across all races/ethnicities; this frequency increased to 6.5%, 2.4%, 1.3%, and 0.6% among persons aged 75 years and older for Caucasians, Asians, Hispanics, and Africans, respectively. Thus, although early AMD was fairly common for Hispanics and Africans, the more advanced form of disease was much less so. Late AMD in Asians was less frequent than in Caucasians, but more common than in Africans and Hispanics. This relatively high prevalence may partly be explained by the higher incidence of polypoidal choroidal vasculopathy in Asians, which is often not

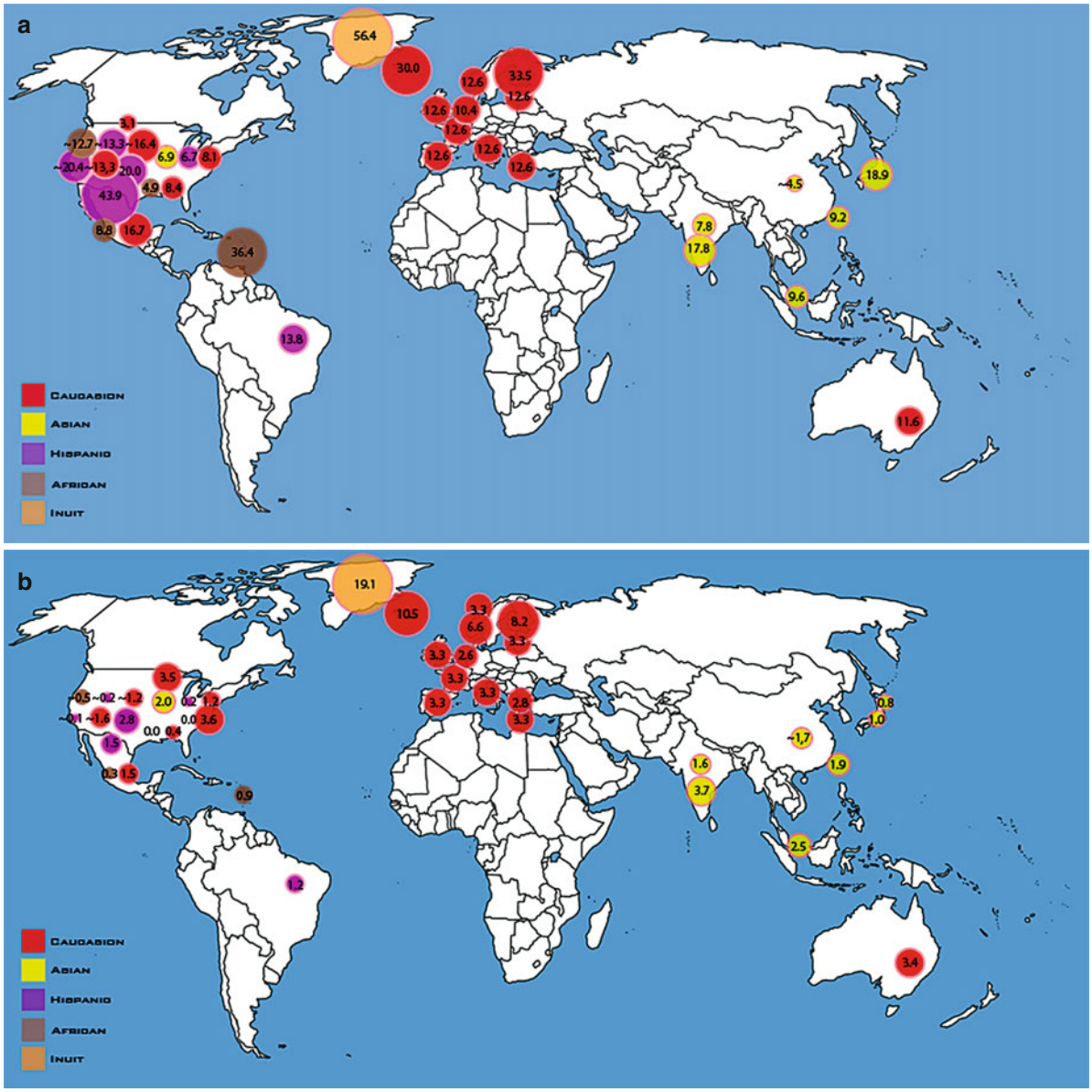


Fig. 1.1 Prevalence of (**a**) early and (**b**) late age-related macular degeneration in persons aged ≥65 years around the world

distinguished from classic neovascular AMD [3–5]. Several studies have reported that polypoidal choroidal vasculopathy accounts for 22.3–24.5% of neovascular AMD in Asian populations [6–8]. An alternative explanation is the rapid economic development and industrialization of certain Asian populations in and outside of Asia, as seen in China and India. This trend may be reflected in a westernization of dietary and other lifestyle habits, e.g., in Taiwan, the average daily calories and fat intake in the past three decades had increased [9–12].

The progression to more advanced AMD in Africans and Hispanics is limited compared with that in Caucasians, despite the relative frequent occurrence of early AMD. The reason for this paradox remains unclear. There could be systematic differences in grading, in sampling techniques, or in age distribution. There may be bias because of higher rate of survival, participation, or gradable photographs for Caucasians compared with Africans and Hispanics. However, it is possible that Africans and Hispanics with their more pigmented choroid and retinal pigment epithelium are

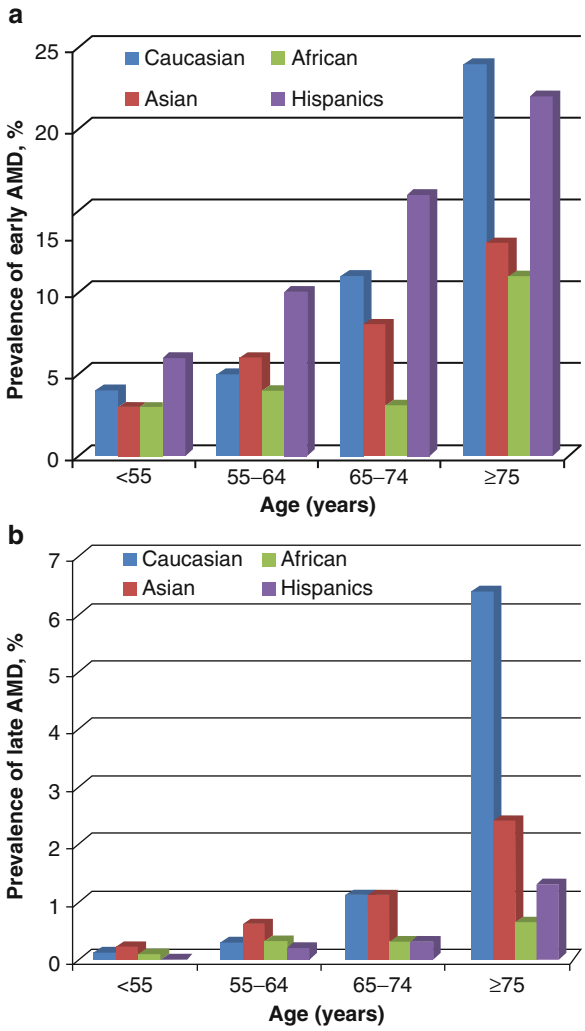


Fig. 1.2 Prevalence of (**a**) early and (**b**) late age-related macular degeneration in various racial/ethnic groups

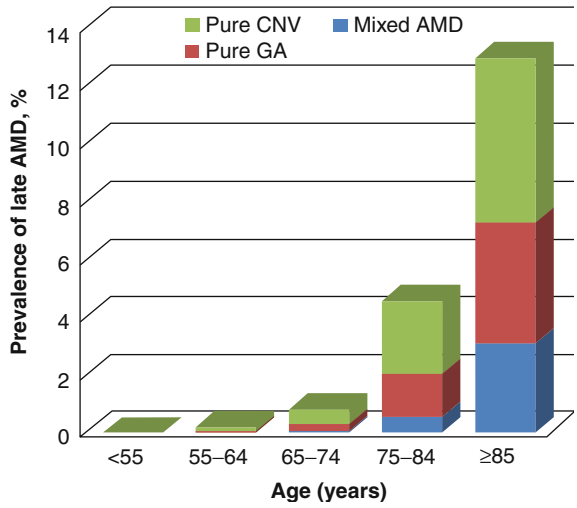


Fig. 1.3 Prevalence of geographic atrophy and neovascular AMD in the three continent study (USA, Europe, and Australia)

at lower risk of late AMD because of the protective effects of melanin against oxidative damage [13, 14]. Another likely explanation for the apparent contradiction is that risk factors may vary in frequency across the races, in particular the genetic variants.

How do the subtypes of AMD relate to age? Three studies with very similar diagnostic criteria, i.e., the Beaver Dam Eye Study (BDES), the Rotterdam Study (RS), and the Blue Mountains Eye Study (BMES), pooled their data to address this issue [15]. The investigators performed consensus grading on all subjects with late AMD, and calculated the individual frequencies of pure geographic atrophy, pure neovascular macular degeneration, and mixed types of macular degeneration. The rise in prevalence of neovascular macular degeneration appears to occur at a slightly earlier age than pure geographic atrophy, followed by mixed forms of macular degeneration (Fig. 1.3).

1.3.2 Incidence

In the last two decades, many incidence studies reported their data, most of which were based on Caucasians [16–28]. Caution is warranted when comparing age-specific incidence rates because a small number of persons or a different distribution of factors such as gender and age within the age strata can affect the precision of estimation. Another limitation is that follow-up times varied widely across the studies.

Given these drawbacks, we extrapolated the data of each study to 10-year incidence rates. The overall 10-year risk estimates were 11.1% in the Hisayama Study, 12.1% in the Beaver Dam Eye Study, 13.9% in the Barbados Eye Study, 14.1% in the Blue Mountains Eye Study, 16.7% in the Rotterdam Study, 17.7% in the Los Angeles Latino Eye Study, and 23.7% in the Copenhagen City Eye Study. The differences in incidence rates between studies may reflect variation in study design, temporal effects, but also real effects due to variation in risk factors. There was no difference in incidence rate between males and females. Stratifying

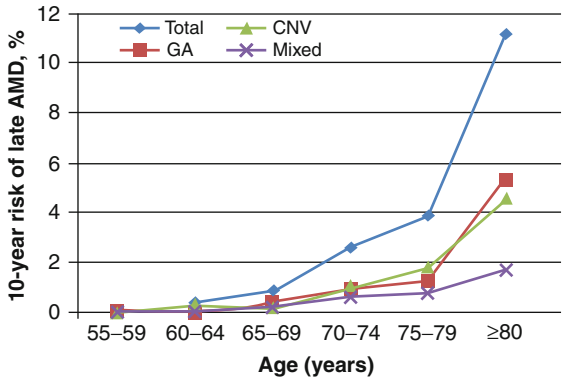


Fig. 1.4 Incidence rates and 10-year risks of the subtypes of late age-related macular degeneration as a function of age in the Rotterdam Study

for subtype in the Rotterdam Study (Fig. 1.4) revealed that the incidence of both pure neovascular AMD and pure geographic atrophy rose steeply after the age of 75 years at similar rates. The incidence of mixed AMD rose later, at the age of 80 years.

1.4 Natural Course

There are several studies that provide data on the natural course of early and late features. All acknowledge that soft drusen and pigmentary abnormalities are the most significant fundus features that increase the risk to develop a late form of AMD. Subjects with these abnormalities have an estimated risk of late AMD between 1.3% and 6.0% per year [16, 17, 19–21, 24–27, 29–38]. In contrast, subjects with only hard drusen <63 μm had no risk of late AMD within a 5-year period [25, 26]. The Rotterdam Study, the Beaver Dam Eye Study, and the Blue Mountains Eye Study, all reported that a large area of any type of drusen in combination with pigment changes carries the highest risk of late AMD [19, 20, 25, 26].

What is the course of the second eye when the first eye has developed late AMD? Several studies have attempted to quantify the risk of late AMD for this eye, and estimates of the 5-year risk of second eye involvement were 30–40% [17, 19–21, 25–27, 33, 39, 40]. The risk of AMD in the fellow eye appears to depend on the profile of features in that eye, similar to development of AMD in the first eye: large areas of drusen, confluence, and pigment changes [19, 25, 26, 41].

Data from the Beaver Dam Study suggests that those with geographic atrophy in the first eye, but not those with neovascular AMD, had a more increased risk of late AMD in the second eye opposed to those who had bilateral early ARM. The type of AMD of the second eye more often appears to match the type of AMD of the first eye, although development of the other type is not uncommon [19, 25, 26, 29, 33, 39] In addition, development of geographic atrophy in eyes with initial neovascularization or vice versa is rather frequent [19, 27, 29, 39, 42–44]. Both these findings suggest that risk factors for these two late-stage disease phenotypes may overlap considerably.

1.5 Genetic Factors

Rapid advances have been made over the past few years in the identification of causative and protective genetic variants associated with AMD. The major breakthroughs have been the discoveries of the complement factor H (*CFH*) gene and the chromosomal 10q26 locus, which contains the *LOC387715* and *HTRA1* genes [45]. These major susceptibility genes are involved in more than 60% of severely affected cases [46], which underscores the pivotal role of the inflammation and oxidative stress pathways in the etiology of AMD. Although they confer a smaller effect, other established genetic risk markers are *C3*, *C2/FB*, *CFI*, and *APOE* [47–49]. Emerging research is focusing on the role of lipid metabolism in AMD.

1.5.1 The Complement Pathway Genes

1.5.1.1 Complement Factor H (CFH)

Genome-wide linkage analyses identified a susceptibility locus on chromosome 1q25-q31 [50–56]. In 2005, the first reports of an association between a genetic variant in the complement pathway and AMD appeared when three groups linked the Y402H allele of the complement factor H (*CFH*) gene on chromosome 1q32 with an increased risk of AMD [57–59]. This finding has since been replicated by numerous studies in different populations (Fig. 1.5) [46, 60–93].

CFH is a key regulator of the complement pathway. Activation of this pathway initiates a proteolytic cascade that releases pro-inflammatory anaphylatoxins

a

Study or Subgroup	Late AMD n	Late AMD N	No AMD n	No AMD N	Weight	Odds Ratio IV, Random, 95% CI	Year
Souied et al.	159	282	55	182	3.3%	2.98 [2.01, 4.43]	2005
Zareparsi et al.	749	1233	186	551	6.3%	3.04 [2.46, 3.75]	2005
Conley et al.	211	336	68	216	3.7%	3.67 [2.56, 5.28]	2005
Magnusson et al.	1488	2660	977	2530	8.5%	2.02 [1.81, 2.25]	2005
Rivera et al.	1404	2332	707	1892	8.2%	2.54 [2.24, 2.87]	2005
Klein et al.	123	190	37	96	2.3%	2.93 [1.76, 4.86]	2005
Edwards et al.	434	790	135	380	5.4%	2.21 [1.72, 2.85]	2005
Hageman et al.	1066	1904	275	806	7.2%	2.46 [2.07, 2.92]	2005
Despriet et al.	203	342	1599	4784	6.0%	2.91 [2.33, 3.64]	2006
Sepp et al.	538	886	190	524	6.0%	2.72 [2.17, 3.40]	2006
Fisher et al.	145	310	107	300	4.2%	1.59 [1.15, 2.19]	2006
Baird et al.	157	238	107	288	3.7%	3.28 [2.29, 4.70]	2006
Seitsonen et al.	435	670	312	700	6.1%	2.30 [1.85, 2.86]	2006
Schaumberg et al.	50	111	136	401	3.0%	1.60 [1.04, 2.45]	2006
Conley et al., CHS	125	252	689	2102	5.2%	2.02 [1.55, 2.63]	2006
Conley et al., AREDS	859	1402	125	350	5.6%	2.85 [2.23, 3.63]	2006
Brantley et al.	207	376	129	378	4.7%	2.36 [1.76, 3.17]	2007
Seddon et al.	361	562	1083	2370	6.7%	2.13 [1.76, 2.58]	2007
Mori et al.	33	376	15	278	1.6%	1.69 [0.90, 3.17]	2007
Losonczy et al.	68	114	46	96	2.1%	1.61 [0.93, 2.78]	2009
Total (95% CI)		**15366**		**19224**	**100.0%**	**2.41 [2.21, 2.64]**	
Total events	8815		6978				

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 47.44$, df = 19 (P = 0.0003); $I^2 = 60\%$
Test for overall effect: Z = 19.55 (P < 0.00001)

Odds Ratio IV, Random, 95% CI
0.2 0.5 1 2 5

b

Study or Subgroup	Early AMD n	Early AMD N	No AMD n	No AMD N	Weight	Odds Ratio IV, Random, 95% CI	Year
Despriet et al.	415	856	2478	7238	28.9%	1.81 [1.57, 2.08]	2006
Tedeschi-Blok et al.	117	570	193	1140	22.5%	1.27 [0.98, 1.64]	2007
Ziskind et al.	17	32	82	196	6.5%	1.58 [0.74, 3.34]	2008
Lin et al.	35	266	16	360	8.8%	3.26 [1.76, 6.02]	2008
Droz et al.	177	312	35	100	12.8%	2.43 [1.52, 3.89]	2008
Losonczy et al.	46	96	63	190	11.7%	1.85 [1.12, 3.06]	2009
Gao et al.	39	416	15	280	8.8%	1.83 [0.99, 3.38]	2010
Total (95% CI)		**2548**		**9504**	**100.0%**	**1.82 [1.47, 2.25]**	
Total events	846		2882				

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 12.31$, df = 6 (P = 0.06); $I^2 = 51\%$
Test for overall effect: Z = 5.50 (P < 0.00001)

Odds Ratio IV, Random, 95% CI
0.2 0.5 1 2 5

Fig. 1.5 Allele-based meta-analysis of association studies investigating *Complement Factor H* Y402H and risk of (**a**) late AMD and (**b**) early AMD, age-related macular degeneration; AREDS, Age-related Eye Disease Study; CHS, Cardiovascular Health Study; CI, confidence interval; IV, inverse variance; n, number of risk alleles; N, total number of alleles; Random, random effects model Conley, Edwards, Hadley, Hageman, Magnusson, Rivera, and Zareparsi et al. included (signs of) early and late AMD in their outcomes. CHS reported data on one eye per person. ORs and 95% CIs were calculated using the random effects model of the DerSimonian and Laird method to accommodate heterogeneity across studies

and stimulates formation of membrane attack complexes leading to cell lysis. CFH inhibits the activation of complement component C3 to C3b and degrades C3b, which limits the amplification phase of the alternative complement cascade [94]. *CFH* Y402H impairs this regulatory function of *CFH* [95–97], leading to

complement overactivation, and thereby increasing the risk of AMD [57–59, 64, 66]. CFH is expressed in the retinal pigment epithelium and the Y402H variant is evidently associated with the presence of complement proteins in drusen [64, 98].

The population attributable risk of Y402H for late AMD is estimated to be between 25% and 70% in Caucasians [46, 58, 59, 61, 66, 68, 71, 83, 91, 99–102], and approximately up to 3.3% in Asians [82, 84]. This implies that the Y402H variant is involved in the vast majority of all cases of AMD in Caucasians, whereas it is involved in a much smaller proportion of cases in Asians and probably other races/ethnicities. As mentioned earlier, the prevalence of Y402H varies greatly among racial/ethnic groups and so does the frequency of AMD. The Y402H variant is much less common in Asians (~10–15%) and Hispanics (~17%), whereas it is equally common in Caucasians and Africans (~36%) [103]. Therefore, additional genetic and/or environmental factors are likely to contribute to the pathogenesis of AMD which might act independently or jointly.

Further dissection of the broader genomic region of *CFH* identified additional susceptibility alleles in strong association with AMD [104–106]. The strong linkage disequilibrium hampered evaluation of single SNP effects, but some differences were observed. Caucasian case-control studies found an association between a noncoding variant (rs1410996) at *CFH* and disease susceptibility that was stronger than for Y402H [104, 105]. In Japanese and Asians populations, the Y402H variant was not significantly associated with AMD, whereas other variants in *CFH* including rs1410996 moderately increased disease risk [72, 89].

CFH and the closely related genes *CFHR1-5* are part of a gene cluster involved in the regulation of complement activation on chromosome 1q32. Because *CFHR1* and *CFHR3* contain a C3-binding site, they may act as competitive inhibitors with *CFH* and dysregulate complement activation. A haplotype carrying a deletion of *CFHR1* and *CFHR3* (delCFHR1/3) had a protective effect against AMD, which was present in 20% of chromosomes of controls and 8% of chromosome of cases [106, 107].The proteins encoded by these genes are absent in serum homozygotes for delCFHR1/3 [106]. Removal of CFHR1 and CFHR3 may reduce competition for the binding of CFH to C3b, enhance inhibitory activity by CFH, and reduce overall activation of the alternative complement cascade. Deletion homozygotes are most frequent in African Americans (16%), less common in Hispanics (6.8%), and least common in European Americans (4.7%) [108]. The high frequency of the *delCFHR1* allele may be one of the explanations for the low prevalence of late AMD in Africans compared with Caucasians. The delCFHR1/3 was not polymorphic (0.01%) in the Chinese population and was not associated with wet AMD or drusen [86].

Figure 1.5a presents a meta-analysis of all studies with data on Y402H, incorporating 7683 late AMD cases and 9,612 controls. Per allele, the OR of late AMD was 2.41 (95% CI, 2.21–2.64). For GA, the overall pooled OR in Caucasians was 2.82 (95% CI, 2.24–3.56). For CNV, the overall OR was 2.47 (95% CI, 2.22–2.74). For early AMD, the OR was 1.82 (95% CI, 1.47–2.25; Fig. 1.5b).

1.5.1.2 Complement Factor B (CFB)/ Complement Component 2 (C2)

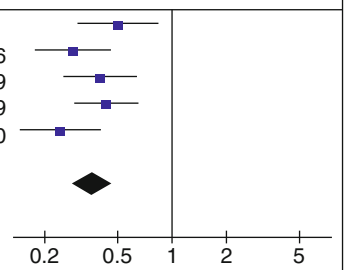
Complement factor B (CFB) and complement component 2 (C2) are activators of the alternative and classical pathways, respectively. Four variants in the *CFB* and *C2* gene located in the major histocompatibility complex III on chromosome 6p21 have been inversely associated with AMD: *CFB* R32Q which is in nearly complete linkage disequilibrium with *C2* IVS10, and *CFB* L9H which is in nearly complete linkage disequilibrium with *C2* E318D [49, 105, 109–114]. Further analyses identified two statistically significant protective haplotypes: the first tagged by the R32Q/IVS10 pair ($P = 2.1 \times 10^{-7}$), and the second by the L9H/E318D pair ($P = 3.4 \times 10^{-6}$). The common haplotype containing the major alleles at these four loci conferred a significant risk for AMD (OR 1.32; $P = 0.0013$). These variants were inversely related to early AMD as well as to both subtypes of late AMD, and also appeared to reduce the rate of progression to more advanced stages of AMD [49, 110].

Genetic and functional data suggest that the *CFB* variants rather than the *C2* variants are likely to cause the observed relation to AMD. The *C2* E318D and IVS10 variants are respectively a conservative change, and a noncoding variant, whereas the *CFB* L9H variant is non-conservative, and *CFB* R32Q results in inferior C3b binding affinity, lower potential to amplify complement activation, and reduced hemolytic activity of the CFB protein [115, 116]. Moreover, the majority of proteins of the alternative pathway (e.g., CFH, CFB) are present in drusen, whereas proteins from the classical pathway (e.g., C2) are not [117, 118]. In addition, after controlling for age, smoking, *CFH* Y402H, and

a

Study or Subgroup	Late AMD n	Late AMD N	No AMD n	No AMD N	Weight	Odds Ratio IV, Random, 95% CI	Year
Rotterdam Study	16	374	356	4364	17.7%	0.50 [0.30, 0.84]	
Gold et al.	25	728	61	550	19.5%	0.29 [0.18, 0.46]	2006
Richardson et al.	29	542	58	470	20.3%	0.40 [0.25, 0.64]	2009
McKay et al.	58	1058	47	398	24.4%	0.43 [0.29, 0.65]	2009
Kaur et al.	22	324	73	316	18.1%	0.24 [0.15, 0.40]	2010
Total (95% CI)		**3026**		**6098**	**100.0%**	**0.36 [0.28, 0.47]**	
Total events	150		595				

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 5.89$, df = 4 (P = 0.21); $I^2 = 32\%$
Test for overall effect: Z = 7.77 (P < 0.00001)



b

Study or Subgroup	Late AMD n	Late AMD N	No AMD n	No AMD N	Weight	Odds Ratio IV, Random, 95% CI	Year
Rotterdam Study	12	374	215	4364	26.4%	0.64 [0.35, 1.16]	
Gold et al.	12	1638	23	546	24.0%	0.17 [0.08, 0.34]	2006
McKay et al.	18	542	24	470	25.7%	0.64 [0.34, 1.19]	2009
Richardson et al.	23	1040	12	336	23.9%	0.61 [0.30, 1.24]	2009
Total (95% CI)		**3594**		**5716**	**100.0%**	**0.46 [0.25, 0.85]**	
Total events	65		274				

Heterogeneity: $Tau^2 = 0.29$; $Chi^2 = 10.69$, df = 3 (P = 0.01); $I^2 = 72\%$
Test for overall effect: Z = 2.47 (P = 0.01)

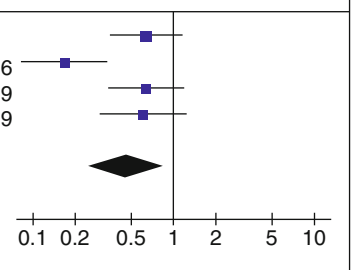


Fig. 1.6 (**a**) Allele-based meta-analysis of association studies investigating *Complement Factor B* R32Q and risk of late AMD. (**b**) Allele-based meta-analysis of all currently available association studies investigating *Complement Factor B* L9H and risk of late AMD age-related macular degeneration; CI, confidence interval; IV, inverse variance; n, number of risk alleles; N, total number of alleles; Random, random effects model. ORs and 95% CIs were calculated using the random effects model of the DerSimoninian and Laird method

LOC387715 A69S, the association with *C2* R32Q proved to be robust (OR, 0.21; 95% CI, 0.11–0.39) while the association with *C2* E318D became insignificant (OR, 0.60; 95% CI, 0.25–1.47) [111]. Stepwise logistic regression also excluded the *C2* IVS10 in favor of *CFB* R32Q [105]. These data suggest that the *C2* variants show residual association with AMD originating from their high linkage disequilibrium with *CFB*. Because the major histocompatibility complex III region consists of many genes involved in inflammation, it is possible that the reported findings are due to high linkage disequilibrium with adjacent loci (e.g., R151Q in the *SKIV2L* gene) [113].

Figure 1.6 presents meta-analyses of all presently available studies for R32Q and L9H. The meta-analysis resulted in a significant OR of 0.36 (95% CI, 0.28–0.47) for the R32Q variant. In the Caucasian studies, the frequencies of the R32Q varied between 4.0% and 5.5% in cases, and between 10.0% and 12.0% in controls. In the Indian study population, the R32Q variant was more common in both cases (7.7%) and controls (23.2%) compared to the Caucasian samples. The meta-analysis also resulted in a significant OR of 0.46 (95% CI, 0.25–0.85) for the L9H variant. In the Indian study, the frequencies of L9H were not significantly different in cases (4.0%) and controls (6.3%; OR 0.61, 95% CI, 0.31–1.22), and the allelic distribution of L9H was not reported. The L9H frequencies in the Caucasian populations varied between 4.0% and 5.5% in cases, and between 10.0% and 12.0% in controls.

Based on the pooled estimates from the meta-analyses, the R32Q appears to have a greater and more consistent protective effect than L9H. Furthermore, a direct functional basis of protection for R32Q has been