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Research Paper

The genetics of age-related macular degeneration (AMD) – Novel targets for designing treatment options?

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ABSTRACT

Age-related macular degeneration (AMD) is a progressive disease of the central retina and the main cause of legal blindness in industrialized countries. Risk to develop the disease is conferred by both individual as well as genetic factors with the latter being increasingly deciphered over the last decade. Therapeutically, striking advances have been made for the treatment of the neovascular form of late stage AMD while for the late stage atrophic form of the disease, which accounts for almost half of the visually impaired, there is currently no effective therapy on the market. This review highlights our current knowledge on the genetic architecture of early and late stage AMD and explores its potential for the discovery of novel, target-guided treatment options. We reflect on current clinical and experimental therapies for all forms of AMD and specifically note a persisting lack of efficacy for treatment in atrophic AMD. We further explore the current insight in AMD-associated genes and pathways and critically question whether this knowledge is suited to design novel treatment options. Specifically, we point out that known genetic factors associated with AMD govern the risk to develop disease and thus may not play a role in its severity or progression. Treatments based on such knowledge appear appropriate rather for prevention than treatment of manifest disease. As a consequence, future research in AMD needs to be greatly focused on approaches relevant to the patients and their medical needs.

1. Medical background of AMD and the need for pharmacotherapy

Age-related macular degeneration (AMD) is the major cause of legal blindness in western countries with over 30 millions of people affected worldwide [1]. The central retina, also known as the macula, is important for visual acuity and color vision and is intimately involved in AMD pathology (Fig. 1A). Initially, patients may experience no symptoms or only a slight distortion of vision while late stages of the disease can lead to a profound loss of central vision and subsequently to legal blindness. Patients can lose their ability to read, to drive a car or even to live independently. The peripheral visual field is often less affected.

While AMD is rarely seen in persons under the age of 50 years, the prevalence increases with age [2,3] and reaches almost 60% in the age group over 90 years [4]. As demographic trends toward an even longer life span in the industrialized countries are expected over the next 20–30 years, this will further increase the number of patients in the near future.

The early stages of the disease are characterized by the accumulation of extracellular material, so-called "drusen", between the retinal pigment epithelium (RPE) and Bruch's membrane. Drusen are visible in the macular area on ophthalmoscopy as small yellowish spots often accompanied by RPE hyper- or hypopigmentation (Fig. 1B). Over time, AMD may progress to late stage disease manifesting as geographic atrophy (GA) which appears as a sharply delineated area with loss of RPE and photoreceptor cells (Fig. 1C).

Abbreviations: AMD, age-related macular degeneration; RPE, retinal pigment epithelium; GA, geographic atrophy; CNV, choroidal neovascularization; VEGF, vascular endothelial growth factor; GWAS, genome-wide association study; OR, odds ratio; 95% CI, 95% confidence intervals; ABCA4, ATP-binding cassette, sub-family A (ABC1), member 4; APOE, apolipoprotein E; CFH, complement factor H; ARMS2, age-related maculopathy susceptibility 2; HTRA1, high-temperature requirement A serine peptidase 1; C3, complement component 3; C2, complement component 2; CFB, complement factor H; CFI, complement factor I; CFD, complement factor F; C5, complement component 5; IAMDGC, International AMD genomics consortium; mTOR, mechanistic target of rapamycin; CYP3A4, cytochrome P450 3A4; CNTF, ciliary neurotrophic factor; PDGF, platelet-derived growth factor; ANG2, angiopoietin 2; AREDS, age-related eye disease study; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; MP, metalloproteases; RPE65, retinal pigment epithelium-specific 65 kDa; MPOD, macular pigment optical density; OCT, optical coherence tomography.

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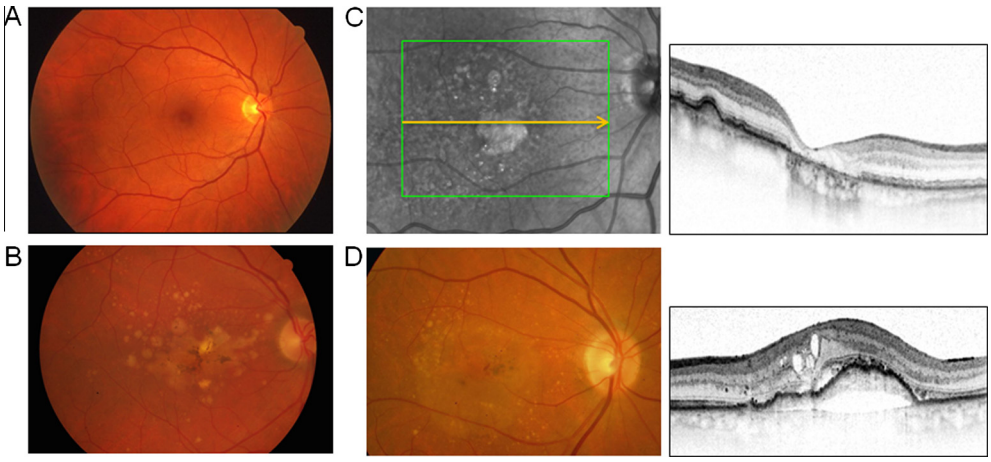

Fig. 1. Clinical images of early and late stage age-related macular degeneration (AMD). (A) Normal macula. (B) Funduscopy of intermediate AMD with large drusen. (C) Infrared image of a macula with geographic atrophy. The orange arrow indicates the section for the optical coherence tomography (OCT) image. The corresponding OCT image (right) shows drusen and the geographic atrophy. In this part the underlying choroid is better visualized. (D) Funduscopic image of a macula with neovascular AMD. The choroidal neovascularization is difficult to identify. Its presence is indicated by a small hemorrhage and a grayish color. The corresponding OCT image (right) reveals the choroidal neovascularization and as a sign of an active process intraretinal and subretinal fluid.

Due to the thinning of the retinal layers, the underlying choroidal vessels then become visible. These changes are summarized as "dry" or atrophic AMD with usually a slow progression over years [5]. This is in contrast to "wet" or neovascular AMD which can lead to a very rapid loss of vision. Neovascular AMD is also classified as a late stage disease but can occur at any stage of dry disease. Atrophic AMD can therefore be considered as the underlying ("default") disease of AMD. Neovascular AMD is characterized by choroidal neovascularization (CNV) where new blood vessels are formed in the choroid, break through Bruch's membrane and grow toward the retina often accompanied by fluid accumulation and bleeding (Fig. 1D). If left untreated, a scarring process leads to irreversible loss of vision. To date, only neovascular AMD can be effectively treated by intravitreal injections of antibodies targeting vascular endothelial growth factor (VEGF) [6].

Currently, there is basically no treatment available for the atrophic form of AMD. Also, in the course of treating neovascular AMD, the dry component of the disease is currently not addressed. As a consequence, many patients may advance to atrophic AMD regardless of the type of late stage AMD. This leaves us with a large unmet need for treatment, specifically for the dry component of late stage AMD.

The pathogenesis of AMD is complex and influenced by multiple components involving both environmental factors and genetic predisposition. The strongest non-genetic risk factors for AMD are age and smoking although many others have been identified, in part with conflicting results, e.g. for sunlight-exposure or nutrition [7,8]. Allergy and supplementation with antioxidants and zinc may be protective [9]. The genetic background will be discussed in detail below; however, it should be emphasized that genetic risk variants in genes related to innate immunity and the complement system are of particular importance [10]. Together, the known risk factors point to the involvement of oxidative stress, inflammation and dysregulation of the complement cascade and other immune responses in the pathogenesis of the disease. It should be stressed, however, that disease manifestations occur late in life implying only subtle effects and chronic mechanisms elicited by the risk factors. This and the lack of suitable animal models [11] pose difficulties in deciphering the precise mechanisms of disease and thus identifying novel target-oriented therapeutic treatments.

2. Synopsis of AMD genetics

2.1. A short introduction to genetic association studies and statistical genetics

Earlier studies intended to delineate the genetic contribution to a disease mostly aimed to find genetic variants segregating with Mendelian disease traits in large families comprising several affected and unaffected individuals (an approach known as genetic linkage analysis). This approach has been extended in recent years to include genetic association studies where diseased, unrelated individuals (cases) and unrelated individuals free of the disease under consideration (controls) are genotyped for genetic variants [12]. Subsequently, the frequencies of the genetic variants are then compared between cases and controls with the appropriate statistical methods (e.g. Armitage trend test or logistic regression). For such studies, sample sizes for cases and controls can range from below 100 to up to several thousand or hundreds of thousands of probands. Furthermore, any number of genetic variants (up to a couple of millions) can be genotyped across the genome, such approaches are then referred to as genome-wide association studies (GWAS) and variants that show an association with a *p*-value lower than 5.0×10^{-8} are generally considered to be significant on a genome wide level. Such a conservative threshold of significance is not required when analyzing only few variants although adequate corrections for multiple testing need always to be considered [13].

Generally, the risk altering properties of a variant are estimated by odds ratios (ORs) per allele and confidence intervals for this estimate are given to show the uncertainty of the estimate, i.e. a 95% confidence interval (95% CI) indicates that in 95 out of 100 times ORs will lie within the boundaries of the confidence interval if the same experiment is being repeated 100 times with a given same sample size. This is, however, only true if few genetic variants are under investigation [14]. An OR of 1.0 suggests no alteration of the risk while an OR below 1.0 implies that this allele of the variant confers a reduced risk for the disease. In contrast, an OR exceeding 1.0 argues for an increased risk. The strength of risk altering properties scales with the OR, i.e. ORs over 2.0 and below 0.5 are considered to be indicators of a strong influence on risk. Regularly, the effect sizes for *common variants* associated with complex