THE MODERN VIEW OF THE STATE OF THE PROBLEM OF AGE-MACULAR DEGENERATION, ITS CONNECTION WITH GENETICS

Yosip Saldan

Age-related macular degeneration (AMD) is now recognized as a complex genetic condition in which any number of genes influence a person's susceptibility to developing the disorder. Earlier studies of genetics, in addition to population-based genetic epidemiologic approaches, strongly emphasized the importance of genetics in AMD. Although the degree of heritability and the number of genes are related, the behavioural and genetic variability of the disease remains unclear, but access to modern diagnostic methods, ophthalmological and molecular genetics, expands our understanding of the mechanisms of its development and progression. One of the main problems of ophthalmological research in the coming years will be to determine the genetic cause of AMD. The use of various genetic methods provides the best chance of determining the function of one or more genes in the pathophysiology of this condition.

The aim of this article is to conduct an analysis of the current literature to understand the pathogenesis of AMD at the molecular level and to provide the opportunity to establish and investigate new treatment methods, as well as to provide a treatment strategy that combines nutritional, environmental, and pharmacological methods to reduce the effect of genetic susceptibility and preserve vision.

Materials and methods - sources of information in the form of scientific articles, research works and monographs were selected for the analytical review of the literature. Databases such as PubMed, Google Scholar, Scopus and Web Of Science were used.

Research results - in the analytical review of modern domestic and foreign literature, it was determined that the use of various genetic methods provides the best chances to determine the function of one or more genes in the pathophysiology of age-related macular degeneration.

Conclusions - one of the main problems of ophthalmological research in the coming years will be to determine the genetic cause of AMD. The use of various genetic methods provides the best chance of determining the function of one or more genes in the pathophysiology of this condition. The goals are to identify people at high risk of developing AMD before they develop symptoms or serious pathology, to understand the pathogenesis of AMD at the molecular level and to enable the establishment and investigation of new treatments, as well as to provide a treatment strategy that combines nutritional, environmental, and pharmacological methods to reduce the effect of genetic susceptibility and preserve vision.

Keywords: age-related macular degeneration, Alzheimer's disease, genetics

How to cite:

© The Author(s) 2023
This is an open access article under the Creative Commons CC BY license

1. Introduction
Numerous sources in ophthalmic research span over eighty years. Despite numerous mentions in the ophthalmological literature more than 150 years ago [1], the genetic cause (AMD) remains largely unknown among ophthalmologists and geneticists.

The growing search for and knowledge in this field of research is primarily due to the growing recognition of the importance of genes in a variety of complex late-onset diseases, as well as the emergence of new technologies that allow scientists to identify genes that influence disease susceptibility.

Within the framework of this part presented at the AMD symposium, we reviewed the evidence supporting a genetic cause of AMD, techniques and methods for identifying AMD susceptibility sites, and additional molecular techniques relevant to understanding the etiology of AMD.

2. Materials and methods
Sources of information in the form of scientific articles, research works, monographs were selected for the analytical review of the literature. Databases such as PubMed, Google Scholar, Scopus and Web Of Science were used.

3. Results
Analytical review of modern literary data on problematic issues of AMD diagnosis was carried out. AMD is a disorder that causes both continuous and terminal
changes that often mask underlying problems. A categorization method [2] that is suitable for epidemiological studies or clinical trials on AMD may not be suitable for genetic evaluation. Evaluation of eye pathology can give an approximate estimate of the severity of the disease. A variety of eye diseases have similar characteristics of terminal atrophy of the pigmented epithelium or choroidal scarring, which may resemble the manifestations of AMD.

The Beaver Dam study found that patients with mild drusen had a significantly higher chance of progressing to more severe stages of AMD [3].

However, geographic atrophy or choroidal neovascular membranes may occur in the absence of soft drusen. Are macular images an adequate tool for describing AMD, or can this approach ignore key outer retinal pathology?

The problems with the AMD phenotype are like those faced by Alzheimer's disease researchers. Like AMD, many patients with Alzheimer's disease have an unusually accelerated progression of dementia and its onset at a young age. Early studies were unable to determine the average course of the disease for the more common types of late-onset Alzheimer's disease. For twenty-five years, this "positive identification" technique was largely neglected in the United States, where Alzheimer's disease was considered an exclusionary diagnosis, resulting in considerable phenotypic variability within the Alzheimer's disease class.

Two things changed this: the initial breakthrough was the discovery that the neurotransmitter abnormalities in Alzheimer's disease were specific, meaning that Alzheimer's disease is not a universal form of neurodegeneration, but rather a more specific entity, a disease [4]. A different conclusion was drawn by Marshall Folstein and John Breitbart, who used "positive identification" methodology to identify a case of "senile neurodegeneration of the Alzheimer type" that showed significant familial linkage [5]. The introduction of survival analytical tools has helped to show the familial nature of "true" Alzheimer's disease.

Another concern is whether the different clinical manifestations of AMD, defined by the presence or absence of drusen, type of drusen, secondary sequelae, appearance of geographic atrophy and/or choroidal neovascular membrane, can be used to differentiate between different hereditary types of AMD. Stargardt disease [6–8] and peripherin-related diseases [9] are two inherited macular dystrophies known to run in many families. Best's disease has low penetrance and varies in expression in families. Studies of AMD in monozygotic twins have revealed significant overlap in the clinical characteristics of AMD, indicating that unique phenotypes may exist in families [10].

Accumulating evidence from twin studies, based on population segregation studies such as the Beaver Dam study [11] and the Framingham study [12], as well as family association studies, make strong claims for the contribution of genetics to AMD. However, they provide only rough estimates of the level of detail and breadth of AMD genetics. Apparently, there are only a few cases of studies of monzygous and heterozygous AMD variants [13] with demonstrated genetic analysis of zygosity.

Meyers [14] found AMD correlates in 23 of 23 monozygotic and 2 of 8 dizygotic pairs of participants, including one dizygotic pair that was inconsistent for central laminar drusen. Klein et al. [14] found that eight of nine pairs of monozygotic twins showed identical fundus characteristics and degree of visual impairment. In the ninth pair, one twin had severe exudative AMD with loss of vision in one eye, while the other twin had massive consolidated drusen and excellent vision in both eyes. Unlike Alzheimer's disease, there have been no rigorous studies based on twin populations to assess the degree of heritability of AMD.

In addition, four similar studies of Alzheimer's disease were conducted [15, 16]. Three studies involved people of all ages, including people prone to developing Alzheimer's disease. The first three showed that genes account for 60-75 % of the total heterogeneity in Alzheimer's disease risk. The latter showed significantly lower heritability. When evaluating these data, it is important to understand that "heritability" is a proportion, not an absolute amount.

Drs Klaiver and de Jong [17–19] completed an equivalent study involving 101 patients with end-stage AMD and 154 randomly selected participants who did not have AMD. They found that relatives of patients had an odds ratio of 4.8 (95 % CI 1.8-12.2) for initial AMD and an odds ratio of 19.8 (95 % CI 3.1-126) for end-stage AMD. The risk ratio of early AMD changes in the offspring of patients was 6.6 (95 % CI 1.4-31.8). Surprisingly, no offspring of AMD patients were found to have end-stage AMD.

Overall, 76 % of participants with a family history of AMD had a genetic component to the disease, and 23 % of those with end-stage AMD could be attributed to a genetic basis [20, 21].

Apolipoprotein E has recently been associated with AMD due to a lower frequency of the epsilon allele in individuals with exudative AMD compared to controls [22–24]. Similar observations, as well as signs of ApoE protein within AMD-associated aggregates in the macula, were described by Claver and colleagues [25–27]. This may be the reverse of what occurs in Alzheimer's disease, where a person's genotype at the APOE polymorphism locus (which produces the protein apolipoprotein E) significantly predicts the age at which susceptible individuals may develop Alzheimer's disease [28–30]. The epsilon allele (one of three normal variations) tends to accelerate the onset of Alzheimer's disease in certain cases.

This accelerates the age-related incidence and incidence of Alzheimer's disease among people with the epsilon allele, especially in epsilon. Thus, the APOE epsilon allele was previously identified as a determinant component of Alzheimer's disease in epidemiologic studies but was later shown to be a modelling gene. It is worth noting that the association between APOE and Alzheimer's disease was detected using a nonparametric association study, demonstrating that this method can effectively find associations in addition to gene modification associated with a complex genetic disease.

In complex age-related diseases, genes may act through different mechanisms (whether alone or in combination with environmental variables). It is important to look at demographics to decide whether ge-
genetics are exposure modifiers or underlying elements of susceptibility.

Many researchers rely on nonparametric linkage analysis alongside many relatively few families with AMD (two or more individuals with the disease, usually siblings) to evaluate potential genes and genetic loci associated with traditional macular dystrophies, in addition to investigating any genetic loci that may influence susceptibility to AMD. The non-parametric method makes it possible to investigate the possibility of association of a genetic locus with AMD without choosing the type of inheritance (dominant or recessive) and without interfering with gene variation. The idea is simple – if a pair of relatives (such as siblings or cousins) have AMD, then the genetic factors that cause susceptibility to AMD are likely to be among the traits shared by those people.

When we study several of these families, the common areas that specifically cause AMD will be seen with advantage, surpassing random chance. With a sufficiently large number of families, it is possible to identify even a modest genetic locus that causes AMD (either in a small proportion of families, or because it has little effect). The number of families to be analyzed depends on the complexity of the genetics of the disease. Although we can run simulations to predict the power to find association of AMD with a significant locus [31, 32], we do not know how many families to study until statistical tests of association are evaluated.

In theory, regardless of whether multiple genes contribute to AMD, the role of a particular locus can be determined by analyzing a sufficient number of families. When one analyzes many families, one may simply miss a locus that contains a gene that causes only a small proportion of AMD cases. An illustration of this problem is Dr. Stone's attempts to find a link between the GLCA1 locus and open-angle glaucoma in adults. He successfully demonstrated that a polymorphism in the gene associated with GLCA1 is responsible for approximately 4% of cases of open-angle glaucoma, even though a non-parametric analysis of glaucoma showed no correlation with this locus.

Horin et al. used 120 AMD families to conduct a 20 cM autosomal genome-wide search for AMD susceptibility genes. A rating system was used to establish the diagnosis of AMD, which measured the severity of macular corrections and the likelihood of the underlying disorder, AMD, compared to alternative explanations for macular degeneration. About sixty-five percent of those surveyed had a choroidal neovascularization that was characteristic of their disease, with the technique of verification mainly by ophthalmology and vitreoretinal practice.

There was no evidence of correlation with any of the recognized macular dystrophy or retinal dystrophy loci, suggesting that no single hereditary macular dystrophy is responsible for a significant proportion of AMD cases. Although the initial identification of multiple AMD susceptibility loci by the first whole genome scan and the second, 10 cM whole genome scan with 240 families, confirmatory studies with larger numbers of families and biomarkers failed to establish sufficient evidence of linkage at a single locus. As a result, although this technique continues to have the potential to identify loci associated with AMD, it has not yet yielded results. This may be due to the genetic variability of this group of diseases, with each gene accounting for less than 5–10% of the familial AMD population.

This limitation can be addressed in the future by evaluating more families or working with groups with less genetic variation.

It is a common misconception that a disorder with a strong hereditary basis should manifest itself independently of environmental circumstances. Genetic vulnerability and genetic determinism are commonly confused. For example, epidemiological evidence indicates that smoking is a significant risk factor for AMD [33–35], while additional dietary variables are also associated [36].

Again, the disorder provides an opportunity to examine environmental variables that may influence age of onset or risk of disease. At least four environmental factors (smoking, use of nonsteroidal anti-inflammatory drugs, hormone replacement therapy, and antioxidant vitamins) may influence the genetic risk of Alzheimer's disease. Studies of identical twin or sibling pairs have provided some of the strongest evidence for these effects [16, 37]. In this scenario, controlling for genes provides clear advantages in case-control designs, as such studies largely avoid confounding with genes. They also allow examination of environmental variables that directly affect onset (rather than risk).

Co-twin and sibling approaches have great potential to identify risk indicators for developing AMD along with other complicated diseases [38]. Once important genes have been identified, frequency (or even careful prevalence) studies can be performed to demonstrate the effects of these genes at the population level. As additional genes are identified, certain phenotypes (clinical characteristics, age of onset, likelihood of progression to atrophy or choroidal neovascular membranes) may be associated with underlying genetic variation. APOE polymorphisms currently appear to influence Alzheimer’s onset but not susceptibility. [39] Various publishers have (in our view incorrectly) labelled APOE as a "major susceptibility locus for Alzheimer's disease". In fact, APOE affects onset and thus age-related risk, but not susceptibility in the most general sense.

Analytical review of modern literary data on problematic issues of AMD diagnosis was carried out. The approaches and main directions of diagnosis of AMD at the current stage are formulated. The use of different genetic methods has been found to provide the best chance of determining the function of one or more genes in the pathophysiology of age-related macular degeneration. The insufficient diagnostic value of existing laboratory tests leads to defects in the registry and monitoring of this disease, the impossibility of an unambiguous assessment of the existing epidemiological situation in various health care systems and further effective implementation of preventive measures.

4. Conclusions

One of the main problems of ophthalmological research in the coming years will be to determine the genetic cause of AMD. The use of various genetic
methods provides the best chance of determining the function of one or more genes in the pathophysiology of this condition. The goals are to identify people at high risk of developing AMD before they develop symptoms or serious pathology, to understand the pathogenesis of AMD at the molecular level and to enable the establishment and investigation of new treatments, as well as to provide a treatment strategy that combines nutritional, environmental, and pharmacological methods to reduce the effect of genetic susceptibility and preserve vision.

Conflict of interests
The authors declare that they have no conflict of interest in relation to this study, including financial, personal, authorship, or any other, that could affect the study and its results presented in this article.

Funding
The study was conducted without financial support.

Data availability
The manuscript has no associated data.

References


Received date 04.02.2023
Accepted date 16.03.2023
Published date 31.03.2023

Yosip Saldan, Doctor of Medical Sciences, Professor, Department of Ophthalmology, National Pirogov Memorial Medical University, Vinnytsya, Pyrohova str., 56, Vinnytsya, Ukraine, 21018
E-mail: osamabestlover@gmail.com