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THE ROLE OF GENETIC FACTORS IN THE PATHOGENESIS OF AGE RELATED MACULAR

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ANNOTATION

Age-related macular degeneration is part of the group of diseases called degenerative maculopathies (macular degenerations). Specifically, the age-related form is the most frequent, especially in women, and appears from the sixth decade of the person's life onwards. It appears bilaterally, although not always with the same severity. It affects the macula, which is the central part of the eye where distinct, high-resolution vision has its seat.

The pathological picture is rather complicated, comprising several alterations (drusen formation, retinal neovascularization, detachment of the pigment epithelium), which can occur either individually or simultaneously and, if not detected in time and treated, lead to blindness.

The results obtained open up new prospects for understanding the pathogenesis of AMD, which will help develop an active medical management system for patients at the outpatient stage with the determination of individual risks for the development and progression of AMD, the appointment of individual preventive measures for both the patients themselves and their families.

Keywords: *age-related macular degeneration; pathogenesis; complement factor H gene; genes HTRA1, ARMS2/LOC387715, PLEKHA1.*

INTRODUCTION

Age-related macular degeneration (AMD) is one of the most common eye diseases and is the leading cause of vision loss in people over 40 years of age. According to the World Health Organization, 161 million people in the world suffer from eye diseases, including 25-30 million people affected by AMD.

The article presents an overview of studies on the role of genetic factors in the pathogenesis of age-related macular degeneration. The Y402H polymorphisms of the complement factor H gene, HTRA1, ARMS2/LOC387715, and PLEKHA1 increase the risk of developing age-related macular degeneration. Other genes that have been identified to date are described in more detail. Possible schemes of the influence of mutations in these genes on the onset and progression of age-related macular degeneration are considered.

The article presents the results of studying the association of ARMS2, CFH and VEGFA gene polymorphisms with age-related macular degeneration in the population. Studies have proven the association of polymorphic genotypes and alleles rs10490924 of the ARMS2 gene, rs800292 of the CFH gene and rs2010963 of the VEGFA gene with the development of AMD inpatients.

Genetic studies of the development of central retinal dystrophy are timely due to the key role of genetic mutations in the pathogenesis of age-related macular degeneration (AMD), one of the most urgent problems of modern ophthalmology. Age-related macular degeneration (AMD) apparently leads to primary disability in 11%is the leading cause of the irreversible decline in people of working age and in 28%vision among the population over 59 years of age, as in Western-resident patients [1]. Diseases of recent years to an increase in durationing has a steadily progressing course, the number of AMD will beproceeds with damage to the macular area and grows steadily [24].

Involvement in the pathological process of pigmentary risk Factors for the development of retinal epithelium (PES), Bruch’s membrane, as well assame layer of choriocapillaries, eventually leads to loss of central vision.

To date, despite the manyresearch on AMD, etiological the history and pathogenesis of this disease remainnot fully educated.

Both eyes are affected in 61% of caseswhich leads to primary disability in 12%people of working age and 27% moreresidential patients [4, 5]. Due to the trendrecent years to an increase in durationlife in the world, the number of AMD will begrow steadily [21].

Purpose:

To determine which genes cause the dry form of AMD in our region and to study their pharmacogenetic properties.

Methods:

Over the past 16 years, scientists have been trying toestablish the genetic changes underlying the development of AMD.

Numerous studies have demonstrated the family, hereditary nature of the process of development of this disease. According to J.D. Gass, family history is an important risk factor in 22% of patients with AMD. A threefold increase in the risk of developing AMD has been established if the disease occurs in relatives in the first generation [19]. In addition, there is a strict correspondence between the course of the disease in monozygotic twins [13]. For example, J.M. Seddon provides information on the clinical manifestations of AMD in several generations of a large family [23].

R. Klein et al described a family consisting of 20 people, 9 of whom were diagnosed with a “dry” form of age-related macular degeneration with phenotypic manifestations — multiple drusen and geographic atrophy of RPE [17].

The complexity of identifying genetic mutations is due to the peculiarities of the development of AMD. The disease occurs in the elderly, so it is possible to study only one generation. Parents are usually already dead, and children are still too young for the onset of this disease. Phenotypic heterogeneity of AMD also causes difficulties.

To date, it is known that about 50 genes can be responsible for the development of age-related macular degeneration. However, a highly significant association with the development and progression of the disease was established only in a few of them.

Various approaches have been used to identify the exact region of the genome that plays an important role in the pathogenesis of AMD. The initial strategy was to study the genes involved in the development of hereditary macular dystrophies, which had clinical manifestations similar to those of AMD [9, 12]. However, it cannot be reliably stated that most of these genes are in any way associated with the development of AMD.

For example, mutations in the ABcA4 (ABcR) gene lead to the development of Stargardt's disease. Patients with this pathology become more sensitive to the accumulation of lipofuscin, their family history more often shows the presence of AMD [18]. It still remains unproven that the mutation of this particular gene leads to the development of age-related macular degeneration in such patients [18, 16].

In 2003, scientists identified the first gene likely to play a role in the development of age-related macular degeneration. This gene is Hemicentin-1 (HMcn1)/Fibulin-6 (FBLn6), located on the long arm of chromosome 1 (1q25.3–31.1) [17]. In 2004, another gene was discovered that may be involved in the development of AMD. It also belongs to fibulins, Fibulin-5 (FBLn5) [14].

Results:

Complement factor H polymorphism T1277C (tyrosine-402 → histidine-402) is strongly associated with both dry and wet AMD and points to a possible role for inflammation in the pathogenesis of AMD.

As a result of a retrospective study of 277 patients with AMD, it was found that in carriers of 5 risk alleles of the complement factor H gene and the ARMS2/LOC387715 gene, the wet form of AMD develops 12.23years earlier than in people without these alleles [15].

On the discovery of the TLR3 gene (L412F), which is involved in the development of the late stage of the dry form of age-related macular degeneration. The L412F (rs377529) polymorphism leads to the replacement of leucitin-412 by phenylalanine [16]. Toll-Like Receptor 3 (TLR3) is a membrane protein that belongs to the group of receptors that ensure the functioning of innate immunity.

TLR3 binds the double-stranded RNA of viruses and thus plays an important role in the body's antiviral defenses. When activated, TLR3 begins to attack infected cells, and in the case of dry AMD, RPE cells are attacked. Mutation of the TLR3 gene, resulting in TLR3 inactivation, helps prevent the death of retinal cells and significantly reduces the risk of RPE geographic atrophy [21]. These data open up new possibilities in the search for alternative treatments for AMD.

The PLEKHA1 gene is expressed in the macular region of the retina. It encodes a protein that plays an important role in the activation of lymphocytes and also regulates cell proliferation . Despite the fact that a relationship has been found between carriers homozygous for the A allele in the PLEKHA1 gene and wet AMD, there is no unambiguous evidence that predisposition to this disease is not also caused by the presence of changes in the HTRA1 and ARMS2/LOC387715 genes located in the same locus.

A total of 366 articles were reviewed, including 64 additional articles extracted from the references and 25 webpages and online databases from different institutions. At the end, only 244 references were included in this review.

Conclusion:

The pathological process in age-related macular degeneration flows individually, however, with the development of the subretinal neovascular membrane, the time factor becomes of key importance. With early diagnosis of this condition and timely treatment, it is possible to avoid the loss of visual functions, achieve long-term remission (temporary attenuation of the process) or its reverse development.

Age-related macular degeneration is a complex multifactorial disease that has an uneven manifestation around the world but with one common denominator, it is increasing and spreading. The economic burden that this disease poses in developed nations will increase in the coming years. Effective preventive therapies need to be developed in the near future. Thanks to the high level of development of modern medicine and genetics, it became possible to take a fresh look at the pathogenesis of many diseases, including AMD.

To date, more than 50 genes are known that are responsible for disturbances in the normal course of metabolic processes in the retina and pigment epithelium. The role of many of them in the pathogenesis of AMD is not completely clear. However, the fact of their direct participation in many pathological processes, including lipid metabolism disorders, the development of oxidative stress, chronic inflammation, and choroidal neovascularization, has been established.

Of particular interest is the violation of mutations in a number of genes that can stop the progression of AMD or reduce the likelihood of its development. In an age of rapidly developing genetic engineering is a promising direction for finding new methods of treatment and prevention of the disease.

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