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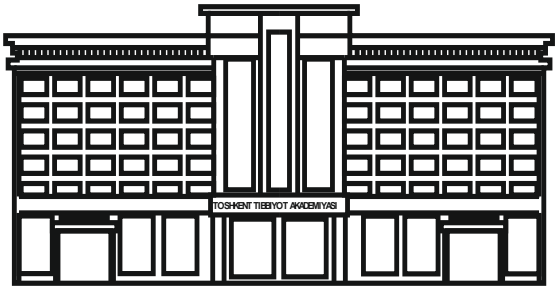

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СОДЕРЖАНИЕ

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GENETIC FACTORS ON THE COURSE OF THE DISEASE IN A NEOVASCULAR FORM OF AGE RELATED MACULODYSTROPHY

Khodjayeva Z.A., Karimova M.X.

ВЛИЯНИЕ ГЕНЕТИЧЕСКИХ ФАКТОРОВ НА ТЕЧЕНИЕ ЗАБОЛЕВАНИЯ ПРИ ВОЗРАСТНОЙ МАКУЛОДИСТРОФИИ

Ходжаева З.А., Каримова М.Х.

YOSHGA BOG'LIQ MAKULADISTROFIYASIDA GENETIK OMILLARNING KASALLIKNING KECHISHIDAGI TA'SIRI

Xodjayeva Z.A., Karimova M.X.

Republican Specialized Scientific and Practical Medical Center for Eye Microsurgery

Представлен анализ роли генетических факторов в патогенезе возрастной макулодистрофии. Показано, что риск развития возрастной макулодистрофии повышают полиморфизмы Y402H гена фактора комплемента H, HTRA1, ARMS2/LOC387715 и. Рассмотрены возможные схемы влияния мутаций в этих генах на возникновение и прогрессирование возрастной макулодистрофии. Кроме того, определенные варианты генов могут оказывать защитное действие против возрастной макулодистрофии, снижая индивидуальный риск развития заболевания. К ним относятся варианты в других частях групп генов комплемента и иммунитета, а также другие гены, влияющие на липиды. Новые данные о патогенезе возрастной макулодистрофии позволят разработать активную лечебную систему ведения больных на амбулаторном этапе с определением индивидуальных рисков развития и прогрессирования заболевания, назначением индивидуальных профилактических мероприятий по как самих пациентов, так и членов их семей.

Ключевые слова: *возрастная дегенерация желтого пятна, патогенез, ген фактора комплемента H, гены HTRA1, ARMS2/LOC387715, PLEKHA1.*

Yoshga bog'liq makula nasli patogenezida genetik omillarning roli tahlili keltirilgan. H, HTRA1, ARMS2/LOC387715 va boshqalar komplement omil genining Y402H polimorfizmlari yoshga bog'liq makula nasli rivojlanishi xavfini oshirishi ko'rsatilgan. Ushbu genlardagi mutatsiyalarning yoshga bog'liq makula degeneratsiyasining paydo bo'lishi va rivojlanishiga ta'sirining mumkin bo'lgan sxemalari ko'rib chiqiladi. Bundan tashqari, ba'zi gen variantlari yoshga bog'liq bo'lgan makula degeneratsiyasidan himoya qilishi mumkin, bu esa odamda kasallikning rivojlanish xavfini kamaytiradi. Bularga komplement va immunitet gen guruhlarining boshqa qismlaridagi variantlar, shuningdek, lipidlarga ta'sir qiluvchi boshqa genlar kiradi. Yoshga bog'liq makula nasli patogenezi bo'yicha yangi ma'lumotlar kasallikning rivojlanishi va rivojlanishi uchun individual xavflarni aniqlash, ikkalasi uchun individual profilaktika choralarini tayinlash bilan ambulatoriya bosqichida bemorlarni davolashning faol tizimini ishlab chiqishga imkon beradi. bemorlarning o'zlari va ularning oilalari.

Kalit so'zlar: *oshga bog'liq makula nasli, patogenezi, komplement omil H geni, genlar HTRA1, ARMS2/LOC387715, PLEKHA1.*

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 [4]. Diseases of recent years to an increase in durationing has a steadily progressing course, the number of AMD will be proceeds with damage to the macular area and grows steadily [22].

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 many research on AMD, etiological the history and pathogenesis of this disease remain not fully educated [6,7].

Both eyes are affected in 61% of cases which leads to primary disability in 12%people of working age and 27% more residential patients [5,20]. Due to the trend recent years to an increase in duration life in the world, the number of AMD will be grow steadily [9,19].

Over the past 16 years, scientists have been trying to establish the genetic changes underlying the development of AMD [1,2].

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 [8,14,21]. In addition, there is a strict correspondence between the course of the disease in monozygotic twins [3,14]. For example, J.M. Seddon provides information on the clinical manifestations of AMD in several generations of a large family [12,24].

R. Klein et al. [23] 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 [16].

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 [13,15,18].

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 [3,10,11]. 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 [15,18]. It still remains unproven that the mutation of this particular gene leads to the development of age-related macular degeneration in such patients [16,17].

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) [23]. In 2004, another gene was discovered that may be involved in the development of AMD. It also belongs to fibulins, Fibulin-5 (FBLn5) [14].

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.

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 [19]. 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.

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.

To date, more than 50 genes are known that are responsible for disturbances in the normal course of metabolic processes in the retinal 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.

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GENETIC FACTORS ON THE COURSE OF THE DISEASE IN A NEOVASCULAR FORM OF AGE RELATED MACULODYSTROPHY

Khodjayeva Z.A., Karimova M.X.

An analysis of the role of genetic factors in the pathogenesis of age-related macular degeneration is presented. It has been shown that the Y402H polymorphisms of the complement factor gene H, HTRA1, ARMS2/LOC387715, etc. increase the risk of developing age-related macular degeneration. Possible schemes of the influence of mutations in these genes on the occurrence and progression of age-related macular degeneration are considered. In addition, certain gene variants may be protective against age-related macular degeneration, reducing an individual's risk of developing the disease. These include variants in other parts of the complement and immunity gene groups, as well as other genes that affect lipids. New data on the pathogenesis of age-related macular degeneration will allow the development of an active treatment system for managing patients at the outpatient stage with the determination of individual risks for the development and progression of the disease, the appointment of individual preventive measures for both the patients themselves and their families.

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