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THE INFLUENCE OF GENETIC FACTORS ON THE COURSE OF THE DISEASE IN AGE RELATED MACULODYSTROPHY

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Annotation. Relevance. The article provides an overview of research on the role of genetic factors in the pathogenesis of age-related macular degeneration. Complement factor H gene Y402H polymorphisms, HTRA1, ARMS2/LOC387715, and PLEKHA1 increase the risk of YMD development. **Purpose of the study.** A retrospective review of possible patterns of gene mutations influencing the onset and progression of YMD over the past 16 years. **Materials and methods.** Retrospective study of genes causing the pathogenesis of age-related macular dystrophy in 277 eyes. **Result and conclusion.** Of particular interest are the disruption of mutations in a number of genes that may halt or reduce the likelihood of developing AMD. In the rapidly developing era, genetic engineering is a promising direction for finding new ways to treat and prevent disease.

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

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ВЛИЯНИЕ ГЕНЕТИЧЕСКИХ ФАКТОРОВ НА ТЕЧЕНИЕ ЗАБОЛЕВАНИЯ ПРИ ВОЗРАСТНОЙ МАКУЛОДИСТРОФИИ

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Аннотация. Актуальность. В статье представлен обзор исследований роли генетических факторов в патогенезе возрастной макулодистрофии (ВМД). Полиморфизмы Y402H гена фактора комплемента H, HTRA1, ARMS2/LOC387715 и PLEKHA1 повышают риск развития ВМД. **Цель исследования.** Ретроспективный обзор возможных моделей генных мутаций, влияющих на начало и прогрессирование ВМД последние 16 лет. **Материалы и методы.** Ретроспективное изучение генов, обуславливающих патогенез возрастной макулодистрофии на 277 глазах. **Результат и заключение.** Особый интерес представляют нарушения мутаций в ряде генов, которые могут остановить или снизить вероятность развития ВМД. В бурно развивающуюся эпоху генная инженерия является перспективным направлением поиска новых способов лечения и профилактики заболеваний.

Ключевые слова: возрастная макулодистрофия; патогенез; ген фактора комплемента H; гены HTRA1, ARMS2/LOC387715, PLEKHA1.

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

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Annotatsiya. Dolzarbligi. Maqolada yoshga bog'liq makula degeneratsiya patogenezida genetik omillarning roli bo'yicha tadqiqotlarning umumiy ko'rinishi keltirilgan. Komplement omil H genining Y402H polimorfizmlari, HTRA1, ARMS2/LOC387715 va PLEKHA1 YMD rivojlanish xavfini oshiradi. **Tadqiqot maqsadi.** Oxirgi 16 yillikdagi gen mutatsiyalarning YMD ning boshlanishi va rivojlanishiga ta'sirining mumkin bo'lgan sxemalari retrospektiv usulda ko'rib chiqish. **Material va uslublar.** Yoshga bog'liq makulodistrofiya patogenezini keltirib chiqaradigan genlarning retrospektiv usulda 277 ko'zda o'rganish kirdi. **Natija va xulosa.** AMD rivojlanishini to'xtatish yoki uning rivojlanish ehtimolini kamaytirishi mumkin bo'lgan bir qator genlardagi mutatsiyalarning buzilishi alohida qiziqish uyg'otadi. Tez rivojlanayotgan davrda genetik muhandislik kasallikni davolash va oldini olishning yangi usullarini topishning istiqbolli yo'nalishi hisoblanadi.

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

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Relevance. 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.

The complement system is a crucial component of the innate immunity against microbial infection. It contains several plasma and membrane-associated proteins that are organized in three activation pathways: the classical, the lectin and the alternative pathways. Upon activation by molecules on the surface of the microorganisms, these pathways result in the formation of unstable protease complexes, named C3-convertases. Both, the classical/lectin pathway C3-convertase, named C4b2b, and the alternative pathway C3-convertase, named C3bBb, are able to cleave the α-chain of C3 generating C3b. Cleavage of C3 results in the exposure of an internal thiolester which is extremely reactive with nucleophiles, that provides C3b with the potential of binding covalently to biological surfaces exposing hydroxyl or amino groups. C3b deposition leads to opsonization for phagocytosis by polymorphonuclear cells and macrophages. In the presence of an additional C3b molecule, the C3-convertases can function as C5-convertases, cleaving C5 and initiating the assembly of the membrane attack complex that leads to complement-mediated lysis. Normally, activation of C3 in the blood is kept at a low level and deposition of C3b and further activation of complement is limited to the surface of pathogens. Not surprisingly, many complement components are regulatory proteins that modulate complement activation and protect host tissues. Several of these regulatory proteins interact with C3 or C4 derivatives and are encoded by closely linked genes that constitute the Regulator of Complement Activation (RCA) gene cluster on human chromosome 1q32. It is generally accepted that these complement regulatory genes share a common ancestor from which they originated by multiple events of gene duplication. Factor H, a plasma protein encoded by one of these RCA genes, is essential to regulate complement activation and to restrict the action of complement to activating surfaces.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 [35]. 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.

Conclusion. 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.

We have reviewed the current knowledge of the structure and function of factor H and illustrated different situations that relate factor H with chronic or infectious disease. Abundant data are now available that define the critical role of factor H in the protection of the host cells and tissues from damage by complement activation. Furthermore, it is now well-established that the C3b/polyanions-binding site located at the C-terminal region of factor H is the most important site for preventing.

Age, female gender, obesity, race, education status, family history, hyperopia, iris color, cigarette smoking, previ- ous cataract surgery, history of cardiovascular and cerebrovascular disease, diabetes, sunlight exposure and many other factors have been shown to be associated with AMD development.

Scientific evidence shows that genes may play a role in the development of nearly 3 out of 4 cases of this devastating eye disease. The genes that have been shown to be associated with AMD are genes encoding complement system components such as CFH, C2, C3, CFB and HTRA1, ARMS2/LOC387715, PLEKHA1.

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 retinaand 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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