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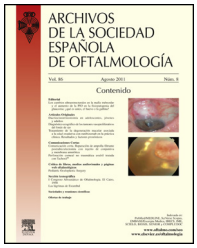

Original article

Influence of CFH, HTRA1 and ARMS2 haplotype polymorphisms in the development of age-related macular disease☆

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ABSTRACT

Objective: To demonstrate genetic influence on the onset of age-related macular disease (AMD), analyzing genotype distribution of haplotypes, including polymorphisms of genes with proved relationships with AMD risk (CFH, ARMS2, HTRA1) in patients with AMD and in healthy people.

Methods: We took 101 consecutive patients with an AMD diagnosis following Wisconsin international classification. For our control group, we took 91 patients without AMD or any significant macular changes. We analyzed CFH rs 1410996, ARMS2 rs 10940923 polymorphisms using real time PCR with Taqman probes, and HTRA1-625 using restriction endonuclease digestion.

We studied haplotypes by simultaneously combining genotypes which, in previous studies, had been shown to have relationship with AMD (CFH, ARMS2, HTRA1) in patients with AMD and healthy people.

Results: There was a statistically significant higher proportion of patients with AMD simultaneously expressing CFH GG (rs 1410996) and ARMS2 TT (rs 10940923) ($p = .037$; OR: 7.742 [1.010–63.156]); ARMS2 TT (rs 10940923) and HTRA 1-625 TT ($p = .001$; OR: 9.006 [2.019–40.168]) and CFH GG (rs 1410996), ARMS2 TT (rs 1040923) and HTRA1-625 GG ($p = .043$; OR: 6.702 [1.003–55.565]) genotypes.

Conclusions: Haplotypes which combine "risk genotypes", demonstrated in previous studies, of our analyzed polymorphisms are more frequent in patients with AMD than in the control group, and they seem to increase the risk of suffering the disease in our population.

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Influencia de haplotipos de polimorfismos de CFH, HTRA1 y ARMS2 en la aparición de degeneración macular asociada a la edad

Palabras clave:
Degeneración macular asociada a la edad
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CFH
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RESUMEN

Propósito: Demostrar la influencia genética en el desarrollo de degeneración macular asociada a la edad (DMAE) analizando las distribuciones genotípicas de haplotipos de polimorfismos de genes con relación demostrada con la aparición de DMAE (CFH, ARMS2, HTRA1) en pacientes con DMAE y personas sanas.

Método: Se tomaron 101 pacientes diagnosticados de DMAE (74 exudativa y 27 atrófica) según las normas del sistema internacional de clasificación Wisconsin. Como control se tomaron 91 pacientes sin DMAE ni otras alteraciones maculares. Se analizó el polimorfismo rs 1410996 del gen CFH, el rs 10940923 de ARMS2 mediante PCR a tiempo real con sondas Taqman y el HTRA1-625 mediante digestión con endonucleasas de restricción.

Se estudió la presencia de haplotipos que combinaban los genotipos que habían demostrado aumentar el riesgo de DMAE de los polimorfismos estudiados de CFH, HTRA1 y ARMS2 en estudios previos en nuestro grupo de pacientes y el grupo control.

Resultados: Se demostró que es más frecuente en el grupo de pacientes, de forma estadísticamente significativa, la expresión simultánea de los genotipos GG de CFH (rs 1410996) y TT de ARMS2 (rs 10940923) (p = 0,037; OR: 7,742 [1,010-63,156]); TT de ARMS2 (rs 10940923) y GG de HTRA1-625 (p = 0,001; OR: 9,006 [2,019-40,168]) y GG de CFH (rs 1410996), TT de ARMS2 (rs 1040923) y GG de HTRA1-625 (p = 0,043; OR: 6,702 [1,003-55,565]).

Conclusiones: La presencia de haplotipos que combinan genotipos, considerados de riesgo en estudios previos, de los polimorfismos analizados es más frecuente en pacientes con DMAE y parece aumentar el riesgo de padecer la enfermedad en nuestra población.

Introduction

Age-related macular disease (AMD) is a disorder of the photoreceptor–retina pigment epithelium–Bruch membrane–choriocapillaries complex.[1–3]

The importance of AMD lies in its prevalence and incidence as it constitutes the main cause of legal blindness in adults of European origin.[4–7] In addition, AMD is the third cause of blindness throughout the world, accounting for 8.7% of all currently blind individuals.[8] In the Western world it is the main cause of irreversible blindness in the age group comprised between 65 and 74 and the second cause in the group between 45 and 69 years of age, although the numbers vary according to the area of the world where studies were carried out. In 2000 it was estimated that, for 54% of all legally blind Caucasian people in the United States over 40 years of age, the cause was AMD followed at a distance by cataracts with 9%. It must be taken into account that these numbers are not applicable to the Afro-American population in which AMD is the third cause of blindness.[9] In Australia it was estimated that the cause of blindness for 13% of legally blind pensioned people was AMD.[10]

Genetic influence in the pathogeny of AMD is determined by means of studies in families and twins.[11–18] Compared with first-degree relatives in families who do not have the disease, first-degree relatives of AMD patients are at greater risk of developing the disease[17] in addition to being affected at an earlier age[16,19] and having greater probabilities of developing advanced AMD.[16]

In order to determine the relative contribution of inheritance and the environment to the etiology of AMD, Seddon et al. carried out a study based on AMD population in twins, including matching and non-matching as well as monozygot and dizygot.[20] Estimates about the inheritability of AMD gave statistically significant results, with a range of between 46% and 71%. These results justified the need to begin a search of genes related to AMD despite the initial difficulties seemingly involved in the genetic analysis of such a complex disease with late expression.

The progress made in the past decade in the study of macular and retinal dystrophy with monogenic inheritance has provided significant pointers to begin a study of AMD genetics. The similarities between the phenotypic expression of hereditary disease which appear early in life with some of the late forms of disease is similar to AMD suggested a potential relationship of candidate genes with AMD. In addition, the said genes were selected on the basis of results of association studies (position criteria) and knowledge on the function of genes (functional criteria). However, this approach has not produced significant developments.[21] Evidence of direct association with the disease has been found in some of the genes.[21] Should these results be confirmed, the variations of said genes would be related to only a small fraction of the vulnerability to the disease.

Complement H factor gene

Multiple analyses of complete genome linking and the meta-analysis of Fisher et al. pointed towards the presence of a