HelmholtzZentrum münchen
German Research Center for Environmental Health

Scientific Highlight April 2010

[X] co-ordinated with the Director of the Institute / Head of Department

Institute / Independent Department / Clinical Co-operation Group / Junior Research Group:
Department of Protein Science

PSP-Element:
G-505700-001

Person to contact for further enquiries:
Elöd Körtvely, elod.kortvely<at>helmholtz-muenchen.de, 3187-3568
Stefanie Hauck, hauck<at>Helmholtz-muenchen.de, 3187-3941
Marius Ueffing, marius.ueffing<at>helmholtz-meunchen.de, 3187-3567

Title of the Highlight:
Toward understanding the genuine function of ARMS2, a protein implicated in age-related macular degeneration (AMD)

Keywords:
extracellular matrix, choriocapillaris, elasticity, fibulin, LOC387715

Central statement of the Highlight in one sentence:
ARMS2 is a secreted protein that binds several matrix proteins including Fibulin-6, and for this latter mutations in the corresponding gene were previously demonstrated to cause familial AMD

Text of the Highlight:

Single nucleotide polymorphisms in chromosomal region 10q26 showed the strongest association with age-related macular degeneration, a leading cause of blindness in the elderly. Recent evidence suggests that in patients homozygous for the risk allele the lack of synthesis of ARMS2 is causative for this disorder.

The pivotal role of the extracellular matrix in the progression of AMD is underlined by the abnormal deposition of extracellular debris (drusen) in macula, observed frequently in affected individuals. Here we show that ARMS2 is a secreted protein that binds several matrix proteins. Notably, ARMS2 directly interacts with Fibulin-6. Mutations in the fibulin-6 gene were previously demonstrated to cause familial AMD. ARMS2 also interacts with further proteins, several of which have been implicated in macular dystrophies. Although ARMS2 lacks any classical targeting sequence, it is translocated to the endoplasmic reticulum in cultured cells prior to secretion. ARMS2 is mostly confined to choroid

pillars, representing a part of extracellular matrix and corresponding to the principal sites of drusen formation. Hence we conclude that ARMS2 may be necessary for proper matrix function.

Publication:
ARMS2 is a constituent of the extracellular matrix providing a link between familial and sporadic age-related macular degenerations.
Kortvely E, Hauck SM, Duetsch G, Gloeckner CJ, Kremmer E, Alge-Priglinger CS, Deeg CA, Ueffing M.
Invest Ophthalmol Vis Sci. 2010 Jan;51(1):79-88.

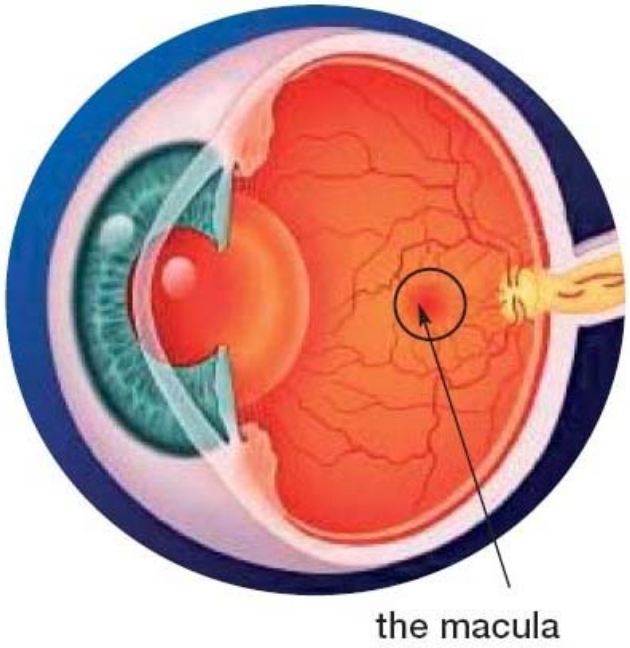
Taking account of the HMGU mission:
Our research aims at gaining better insights into the function of ARMS2 showing the highest association with AMD. This blinding disease affects more than 50 million people worldwide, and there is no effective medication available to cure it. Environmental factors were shown to modulate the onset and the severity of the symptoms. Our work may contribute to translate basic science into modern biomedical therapeutics.

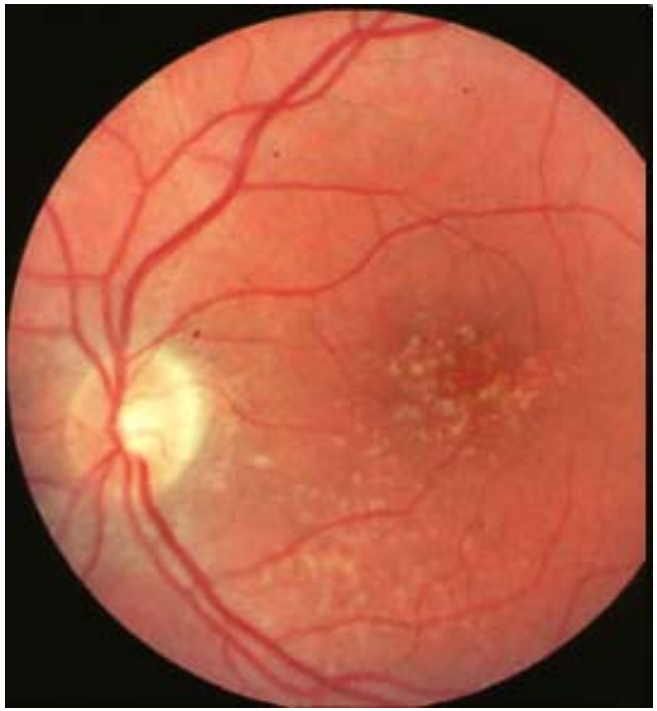
The internal HMGU co-operation partners with whom the Highlight was compiled, if appropriate:

Insights on ARMS2

Department of Protein Science

Getting Closer towards Understanding the Pathogenesis of Age-Related Macular Degeneration





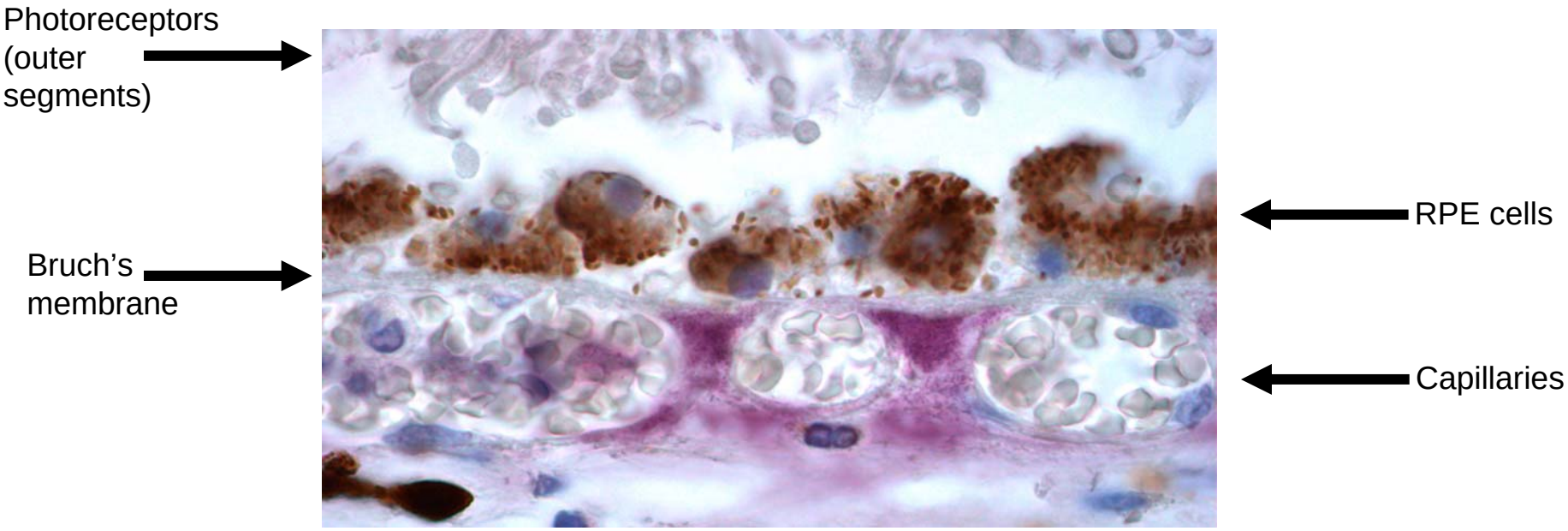
Genetic susceptibility

Risk/protective variants in the following genes

- CFH
- C3
- 10q26 (a cluster of three genes)
  - PLEKHA1 (TAPP1)
  - ARMS2 (LOC387715)
    - Tiny, two-exon gene, short protein (12 kDa)
    - No known domains, function unknown
    - Primate-specific
  - Htra1 (PRSS11)

ARMS2 immunohistochemistry in the eye

ARMS2 is localized to intercapillary pillars (purple staining), which corresponds to the extracellular space separating the smallest capillaries. The dry form of AMD is characterized by the discrete deposition of extracellular debris (drusen) “on top” of the pillars.



Interaction map of proteins related to ARMS2

The names of those proteins, which have already been implicated in diverse macular dystrophies are encircled.

Mutations in fibulin-6 (FBLN6), a direct binding partner of ARMS2, was found to cause familial AMD.