New cause of blindness discovered by scientists

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University of Manchester scientists have discovered a new cause of age-related macular degeneration (AMD), a condition that affects more than 50 million people worldwide and results in blindness.

Professor Tony Day, at Manchester's Wellcome Trust Centre for Cell Matrix Research (WTCCMR), said: "There are several factors that predispose to AMD, smoking being one example.

"More recently it has been discovered that many sufferers are genetically pre-disposed to AMD, but it was not known how it caused the condition. We have unravelled the pathway to show exactly how a very important and common genetic variant affects the eye.

"Our work may now allow the development of new therapeutic strategies for treating or preventing this devastating disease, the most common cause of blindness in the industrialised world."

AMD causes the cells in the back of the eye, within the macula, the central part of the retina that is responsible for our detailed 20:20 vision, to become damaged and cease working. This causes the patient to lose their central vision.

Five years ago it was found that people who have a particular variant of the gene for complement factor H (CFH) have an increased chance of developing AMD. CFH is a protein molecule responsible for regulating part of the immune system, where it has an important role in preventing

damage to our own bodies. It is thought that the AMD-causing form of CFH may not work properly within the eye, but the exact reason for this was not known.

The new study has identified how this dysregulation of the immune system may occur.

Professors Tony Day and Paul Bishop and their team studied eyes given to the Manchester Royal Eye Hospital Eye Bank by donors, after removal of the corneas for transplantation. They found the AMD-related form of CFH cannot localise properly to a layer under the retina called the Bruch's membrane. Having a reduced amount of CFH in this part of the eye would cause or exacerbate local inflammation that would damage cells of the retina and eventually lead to AMD.

The new research, published in the *Journal of Biological Chemistry* and funded by a variety of partners including the Macular Disease Society, Medical Research Council, UMIP and NIHR Manchester Biomedical Research Centre, has also identified that the AMD-form of CFH has impaired ability to bind particular sugar molecules, called GAGs, within the Bruch's membrane, which it is believed will lead to there being insufficient CFH at that site in the eye.

The work provides a novel molecular explanation for AMD which, it is hoped, will lead to new therapeutic strategies for treating or preventing this devastating disease.

Professor Bishop, of the Manchester NIHR Biomedical Research Centre and School of Biomedicine, said: "We think it is possible that a combination of genetics and age-related changes in the structure of complex sugars in the retina triggers AMD.

"We now plan to study the GAG molecules present in the retina in more

detail and see if they change with age and whether this contributes to the progression of AMD. This will provide useful information that will help us in the design and development of new therapies for AMD."

Co-author Dr Simon Clark added: "Our findings are particularly exciting as they would help design a treatment that would prevent, or at least slow down, progression towards, both wet and dry AMD.

"Wet AMD - in which blood vessels grow into the retina - affects 10% of AMD sufferers and there are now treatments that prevent the worsening of this condition. Dry AMD - where the cells in the retina responsible for central vision are slowly destroyed - affects 90% of sufferers, yet there is no treatment available."

Cathy Yelf, head of external relations at the Macular Disease Society said: "This is a significant finding. We knew that CFH was implicated in AMD but we didn't know how. Now we do have one explanation and that is potentially a big step forward in finding new ways to attack AMD. We are delighted to have been able to contribute to this work and offer our thanks and congratulations to the team."

More information: '*Impaired binding of the AMD-associated complement factor H 402H allotype to Bruch's membrane in human retina*', *Journal of Biological Chemistry*.

Provided by University of Manchester