Researchers ID genetic mutation associated with high risk of age-related macular degeneration

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Age- related macular degeneration (AMD) is the leading cause of severe visual loss among the elderly. Researchers had previously identified several relatively common genetic variants which together predict a person's increased risk for AMD, but a significant number of persons without the disease also have these variants. Now, for the first time, investigators have been able to clearly show a specific rare mutation called CFH R1210C that predicts a very high risk of disease and is extremely uncommon among individuals who do not have the disease. Although it is a rare variant, accounting for about 1% of the total cases, it is highly related to familial disease and earlier age of onset. This research is published online and in an upcoming print edition of *Nature Genetics*. The paper is a collaborative effort between investigators from Tufts Medical Center, Tufts University School of Medicine and Brigham and Women's Hospital.

"Our paper shows that there is a genetic variant that confers high risk of the development of AMD; this finding not only clearly links CFH gene dysfunction to disease, but also might help to identify people who need to be screened more closely," said first author, Soumya Raychaudhuri, MD, PhD, a researcher in the Divisions of Genetics and Rheumatology at Brigham and Women's Hospital and an Assistant Professor of Medicine at the Harvard Medical School.

Prior to this publication, it was known that genetic variation within the CFH gene influenced risk of AMD in individuals. In this study, researchers conducted sequencing and genotyping of CFH in 2,423 AMD cases and 1,122 controls in the laboratory of senior author Johanna M. Seddon, MD, ScM, Professor of Ophthalmology at Tufts University School of Medicine and Director of the Ophthalmic Epidemiology and Genetics Service at Tufts Medical Center. They identified a rare, high-risk mutation resulting in an arginine to cysteine substitution in the CFH protein. This mutation is associated with loss of function of the CFH protein and its discovery suggests that loss of CFH function can drive AMD risk. It was associated with advanced AMD with visual loss and many of the patients also had numerous drusen, which are the early hallmarks of AMD.

"The discovery of this rare but penetrant variant strongly associated with disease also points the way to developing new and effective treatments for high risk individuals," said Seddon.

Collaborators in this research included investigators from Massachusetts General Hospital and Johns Hopkins University.

Provided by Brigham and Women's Hospital