RETINA INTERNATIONAL
Seeking A Cure For
Retinitis Pigmentosa, Macular Degeneration,
Usher Syndrome and Allied Retinal Dystrophies

Risk Factors for GA

It is generally thought the causes of GA are multifactorial, caused by the complex interaction of metabolic, genetic and environmental factors.[1] Several risk factors have been strongly associated with the development of GA, most of which are also risk factors for other forms of AMD. These include:

Age: Epidemiological studies show the prevalence of GA increases exponentially with age; some studies have found that GA can affect as many as 1 in 5 people aged >90 years.[2] (See also PREVALENCE DATA - LATE AMD.PDF and INCIDENCE DATA - LATE AMD.PDF for further details of studies reporting prevalence and incidence data for GA.)

Smoking: Smokers are at greater risk factor of developing advanced AMD than non-smokers.[3, 4, 5] A case-control study of 715 white patients found that smoking >40 pack-years of cigarettes was associated with a 3.5-fold greater risk for GA, compared with non-smokers.[4]

Ethnicity: A higher prevalence of GA has been reported in white Europeans, compared with other ethnic groups including Africans, Hispanics and Asians. [6]

Genetic risk factors: Genetic factors play a major role in determining the risk of susceptibility to AMD and progression to late- AMD (GA or neovascular AMD). Large genome-wide association studies have identified over 30 genetic variants associated with the risk of developing AMD.[7] It should be noted that the presence of these genes does not mean that one will inevitably develop AMD, rather one is at higher risk of developing AMD.

[1] Boyer DS, Schmidt-Erfurth U, van Lookeren Campagne M, Henry EC, Brittain C. The Pathophysiology of Geographic Atrophy Secondary to Age-Related Macular Degeneration and the Complement Pathway as a Therapeutic Target. Retina. 2017;37(5): 819-835.
[2] Buch H, Nielsen NV, Vinding T, Jensen GB, Prause JU, la Cour M. 14-year incidence, progression, and visual morbidity of age-related maculopathy: the Copenhagen City Eye Study. Ophthalmology. 2005;112(5): 787-798.
[3] Clemons TE, Milton RC, Klein R, Seddon JM, Ferris FL, 3rd, Age-Related Eye Disease Study Research G. Risk factors for the incidence of Advanced Age-Related Macular Degeneration in the Age-Related Eye Disease Study (AREDS) AREDS report no. 19. Ophthalmology. 2005;112(4): 533-539.
[4] Khan JC, Thurlby DA, Shahid H, Clayton DG, Yates JR, Bradley M, et al. Smoking and age related macular degeneration: the number of pack years of cigarette smoking is a major determinant of risk for both geographic atrophy and choroidal neovascularisation. The British journal of ophthalmology. 2006;90(1): 75-80.
[5] Mitchell P, Wang JJ, Smith W, Leeder SR. Smoking and the 5-year incidence of age-related maculopathy: the Blue Mountains Eye Study. Archives of ophthalmology. 2002;120(10): 1357-1363.
[6] Wong WL, Su X, Li X, Cheung CM, Klein R, Cheng CY, Wong TY. Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. The Lancet Global health. 2014;2(2): e106-116.
[7] Fritsche LG, Igl W, Bailey JN, Grassmann F, Sengupta S, Bragg-Gresham JL, et al. A large genome-wide association study of age-related macular degeneration highlights contributions of rare and common variants. Nature genetics. 2016;48(2): 134-143.

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Of these, genetic variants located at 2 loci – genes associated with the complement cascade on chromosome 1, and the ARMS2/HTRA genes on chromosome 10 – are associated with significantly increased susceptibility to AMD.[8]

The complement cascade is part of the innate immune system that regulates cell death and inflammation. Dysregulation of the complement pathway is believed to play an important role in the development and progression of AMD.[1] Genetic variants in 5 key genes associated with regulation of complement cascade account for 57% of the contribution to disease risk. These include: complement factor H (CFH), complement component 2 and factor B gene (C2/CFB); complement component 3 (C3) and complement factor I (CFI).[9]

In addition to determining the risk of developing AMD or GA, variants of these genes have also been linked to GA progression rates.

[8] Black JR, Clark SJ. Age-related macular degeneration: genome-wide association studies to translation. Genetics in medicine : official journal of the American College of Medical Genetics. 2016;18(4): 283-289.
[9] Fritsche LG, Fariss RN, Stambolian D, Abecasis GR, Curcio CA, Swaroop A. Age-related macular degeneration: genetics and biology coming together. Annual review of genomics and human genetics. 2014;15: 151-171.